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SECOND EDITION

GASTROINTESTINAL ONCOLOGY

A CRITICAL MULTIDISCIPLINARY TEAM APPROACH

JANUSZ A. Z. JANKOWSKI

WILEY Blackwell

Gastrointestinal Oncology

Gastro-intestinal Oncology

A Critical Multidisciplinary Team Approach

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Preface

Why this book, and *why now?* This invited reference book is aimed at a wide spectrum of readers from patients and carers as well as practitioners, specialists and students.

This new volume is unique and aims to satisfy the immediate needs of each reader, while allowing scope and depth for further learning. The editing process for the contributions also works on the premise that information rapidly progresses, so having links to trusted web sources is key to maintain knowledge in an innovative way.

The first edition of this book was awarded many plaudits and reviews including; “written by the leading international experts in the field, it sets the standard in clinical practice” and “the authorship is a mark of quality, this book is a must read”. In the intervening 15 years so much has changed in cancer management and these advances have been reflected in this invited second edition. Specifically, new sections now include the following: the pathophysiology of cancer including sections on diet, probiotics, carcinogens, and genomics; improvements in cancer screening including non-invasive markers, endoscopic imaging as well as histopathological biomarkers; sequential use of advanced imaging modalities; surgical, radiotherapy, chemotherapy and advanced targeted/biological therapies; new psychological and palliative care interventions; new chapters such as sarcoma/stromal tumours, liver transplant, and unknown primary and GI lymphomas.

Each chapter has new boxes for ‘key take home messages’, ‘areas where research and the evidence base is weak’ and an extensive’ reading list of trusted websites for further information’.

In summary this book pushes the training envelope and aims to be both comprehensive in the detail as well as holistic in its management of the patient and their carers. Furthermore, the layout is designed to be easy for fast reference and access by phone or bedside devices for immediate impact at the consultation.

I want to thank all the contributors who have worked tirelessly during the Covid-19 pandemic. They still made time for delivery of uptodate superb contributions, which as so relevant to the post-pandemic world.

So, in ending, I hope you feel purchasing this book, is more of *why not*?

Prof. Janusz A. Z. Jankowski
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Foreword

"The paradigm of a journey from observation to hypothesis testing and then onward to fulfil Koch's postulates."

The discovery 40 years ago of the Helicobacter Pylori organism was a paradigm shift in many ways. Perhaps most importantly as it indicated that the host and the organism have a complex interaction which can lead to disease, not only chronic infection, autoimmunity, but also several forms of cancer. As an adjunctive benefit it showed that we should question any disease causation assumptions which are not evidence based, "Psychiological stress" as a common cause of peptic ulcer disease being the best example.

The journey was long in that it took time to assemble the epidemiological, bacteriological, clinical, oncological teams.

The result was, and still is, to provide the only cure for a condition in gastroenterology, peptic ulcer disease. The benefits also included alleviation of dyspepsia, cures of low-grade gastric MALTOMAs, and prevention of epithelial tumors of the gastric antrum.

This discovery has spawned new interest in fields of research outside the infection-inflammation-cancer sequence, including probiotics, antibiotic resistance, and modulation of host–bacterial interactions.

As I reflect on my career's narrative above, I am therefore glad to see such a large array of multidisciplinary experts working together in this endeavor of *Gastrointestinal Oncology: A Critical Multidisciplinary Team Approach*.

Barry Marshall, December 2022
Nobel Laureate Medicine
University of Western Australia

Section I Upper Gastrointestinal Cancer

1 Epidemiology, Microbiome, and Risk Factors Involved in Carcinogenesis of Esophagus, Gastric, and Intestine

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[Aspects of genomic risk factors are covered in Chapter 2].
[Aspects of relevant colorectal data are covered in Chapter 9].

Introduction

Cancers of the gastrointestinal tract (GIT) encompassing esophagus, stomach, and colorectum make up a significant proportion of cancers diagnosed worldwide and contribute to a considerable burden of disability-adjusted life years and years of life lost. (Kocarnik et al. 2022) The increase of GIT malignancies has been linearly associated with the human development index (HDI), likely due to the adoption of an affluent lifestyle with an increase in the consumption of processed meat, fast food, sedentary lifestyle, smoking, and increasing alcohol consumption. Obesity has become a worldwide pandemic and has been linked to the development of GIT cancers through multiple genetic and epigenetic microenvironment changes. Excess adipokines in obesity mediate a state of chronic inflammation resulting in the activation of multiple pathways that promote carcinogenesis. The understanding of the epidemiology and predisposing factors to GIT cancers is crucial in the development of early detection strategies. Screening efforts such as colonoscopy has reduced the burden of CRC worldwide. Similarly, screening of gastric cancers which has been adopted in Japan and Korea has reduced the numbers as well as improved the survival of gastric cancer.

In this chapter, we will discuss the epidemiology, global time trends, burden of disease, risk factors of esophageal, gastric and intestinal cancer, and strategies to reduce the incidence of these malignancies.

Esophageal Cancer

Epidemiology of Esophageal Cancer

Global Burden and Time Trends of Esophageal Cancer

Esophageal cancer (EC) is the seventh most common cancer globally (Huang et al. 2021) and the sixth leading cause of cancer mortality (Sung et al. 2021). The rates of EC worldwide have increased in the last two decades from 319,969 cases in 1990 to 319,969 cases in 2019 with a relative increase of 67.07% (Li et al. 2021). In 2020 there were 604,100 new cases of EC worldwide with a corresponding age-standardized incidence of 6.3 per 100,000 (Morgan et al. 2022b). The five-year survival of EC remains dismal at less than 20%, owing largely to its late stage of diagnosis (Then et al. 2020). Mortality from EC demonstrated a relative increase of 55.97% from 1990 till 2019 (Li et al. 2021) and resulted in 544,100 deaths in 2020 with a corresponding age-standardized mortality of 5.6 per 100,000 (Morgan et al. 2022b). The highest incidence of EC was observed in East Asia accounting for 59.2% of all EC cases out of which 53.7% occurred in China. EC mortality was observed to be highest in Eastern Asia, accounting for 58.7% of EC-related deaths.

Distribution of Esophageal Adenocarcinoma and Esophageal Squamous Carcinoma

Histologically, EC is divided into adenocarcinoma (EAC) and squamous cell carcinoma (ESCC). The subtype of esophageal cancers varies according to geographic region. ESCC accounts for more than 85% of esophageal cancer cases worldwide (Arnold et al. 2015). There has been a change in the geographic distribution of EC with a rise in EAC, but a reduction in ESCC was noted in Western countries. The incidence rate of ESCC was double in males at 7.8 per 100,000 compared to females at 3.2 per 100,000 (Morgan et al. 2022b). This subtype is commonly seen in regions

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with the highest EC rates, such as Eastern Asia, Southern and Eastern Africa where it constitutes 90% of the EC cases (Zheng et al. 2019). Meanwhile, in American and European countries EAC is predominantly seen (Ilson and van Hillegersberg 2018). The incidence of ESCC is declining, however the incidence of EAC has been increasing in the last decade (Li et al. 2021) primarily due to the increase in the rate of obesity. The commonest anatomical locations of EAC are gastroesophageal junction and cardia (Pohl et al. 2010). The geographic variation demonstrates the multi-hit theory that ethnicity, lifestyle, and genetic factors culminate in the development of EC.

Gender Distribution of Esophageal Cancer

There is a male predominance of EC with 70% of EC occurring in males (Sung et al. 2021). The age-standardized rate (ASR) for EC in males is 9.3 per 100,000 and 3.6 per 100,000 for females globally while the ASR mortality is 8.3 for males and 3.2 for females (Sung et al. 2021). Mortality rates were also observed to be two to three times higher in males, a finding that was most pronounced in Eastern Asia whereby rates of male mortality were eight times higher compared to females (Morgan et al. 2022b). Of note, the male-to-female ratio is highest at ages 50 to 54 and then declines thereafter (Mathieu et al. 2014) suggesting a correlation between androgens and EC and a protective effect of estrogen (Thrift 2021). Androgen receptor expression has been demonstrated in EAC tissue (Kim) (Sukocheva et al. 2015) as well as ESCC tissues (Sukocheva et al. 2015) and may be related to the propagation of its growth. A study by Petrick et al. found a high ratio of androgens to estrogen in patients with EAC. Patients with the highest quartile of androgen to estrogen had 2.4 times increased odds of EAC (Petrick et al. 2018).

Risk Factors for Esophageal Cancer

Barrett's Esophagus and Obesity

The incidence of Barrett's esophagus and obesity has been increasing worldwide which parallels the increase in EAC (Alexandre et al. 2014). Visceral obesity is a significant risk factor for gastroesophageal reflux disease (GERD), Barrett's esophagus (BE) and esophageal adenocarcinoma. Obesity is a state of chronic low-grade inflammation termed meta-inflammation whereby there is an increase in acute phase reactants such as leptin and TNF-a which have mitogenic properties and propagate the progression of Barrett's esophagus to EAC (Corley et al. 2007; Roberts et al. 2010). Adipose tissue had been shown to contain inflammatory cells which synthesize reactive oxygen species which have mitogenic properties (Kim et al. 2012). Leptin, an adipokine, also plays a crucial role in the pathogenesis of obesity induced carcinogenesis. Leptin enhanced cell mitosis and reduced cellular apoptosis via extracellular signal-regulated kinase, p38 mitogen-activated protein kinase, phosphatidylinositol 3′ kinase/Akt and Janus tyrosine kinase 2-dependent activation of cyclooxygenase-2 and prostaglandin E2 production in Barrett's derived EAC lineage of cells (Ogunwobi et al. 2006). Chronic inflammation is associated with epithelial metaplasia and promotes carcinogenesis by creating a microenvironment favorable for tumor development as well as progression (Jankowski et al. 2000). Obesity also exerts mechanical consequences promoting GERD.

GERD has a prevalence of 50% in patients with morbid obesity (El-Serag and Thrift 2021). GERD is the strongest risk factor for the development of Barrett's esophagus. The frequency of GERD symptoms influenced the risk of development of EAC whereby weekly symptoms increased the risk by five-fold (OR 4.92, 95% CI 3.90–6.22) and daily symptoms increased the risk seven-fold (OR 7.40, 95% CI 4.94–11.1) (Rubenstein and Taylor 2010). Barrett's esophagus is defined as the replacement of normal squamous epithelium in the lower esophagus by columnar epithelium with evidence of intestinal metaplasia, the hallmark of which is acid mucin-containing goblet cells. Molecularly, this cellular change heightens the risk of EAC through chronic inflammation. Non-dysplastic BE has the lowest risk of progression to EAC with a rate or progression of 0.3% per year (Hvid-Jensen et al. 2011). Once low-grade or high-grade dysplasia develop, the risk increases. Genomic profiling of BE tissue next to EAC revealed that BE cells have a mutational burden that is only marginally reduced than the median burden for EAC (Alexandrov et al. 2013). Telomere length is altered in chronic inflammation and in patients with BE a shorter telomere length was associated with a higher risk of progression to EAC (Vaughan and Fitzgerald 2015). Obesity and BE have synergistic factors on the development of EAC which explains the rise in the incidence of EAC in the recent years.

Smoking and Alcohol Consumption

Smoking also contributes to the risk of EAC with a robust dose-response association with the number of pack years of smoking (Singh et al. 2013). The risk factors for ESCC differ between Western and Asian population. Cigarette smoking and heavy alcohol consumption are risk factors for ESSC in the West (Pandeya et al. 2013). The OR of ESCC in those who smoked more than 30 pack years was 4.1 (95% CI, 2.7 – 6.2) with the rate being higher in men compared to women (5.5 vs 4.0) (Pandeya et al. 2013), whereas in South East Asia these risk factors were less common; instead, consumption of hot tea, opium, betel chewing, poor diet, low socioeconomic status, and inhalation of aromatic hydrocarbons, a by-product of indoor air pollution, are significant risk factors for the development of ESCC in this region (Sheikh et al. 2019). Heavy alcohol intake defined as more than 170 g per week markedly increased the risk of ESCC but not EAC with a similar dose-response relationship (Pandeya et al. 2009). Concomitant smoking further compounded this risk (Pandeya et al. 2009). Ethanol is the main component of alcohol and is broken down into acetaldehyde which has been classified as a human carcinogen by IAARC (Lachenmeier 2007) and is also a local irritant that promotes DNA methylation thereby promoting carcinogenesis.

Dietary Factors

Dietary risk factors associated with ESCC are increased consumption of *N*-nitroso compounds in men but not in women (Keszei et al. 2013). The N-nitroso compounds are carcinogenic and produce alkyl adducts in the DNA thus promoting mutagenesis (Guttenplan 1990). The risk of ESCC increases in micronutrient deficiencies such as vitamin C, E, folate, (Uhlenhopp et al. 2020) selenium (Steevens et al. 2010), and zinc. Zinc deficiency potentiates the carcinogenic effect of nitrosamines thereby promoting ESCC (Abnet et al. 2005). Other environmental factors that contribute to the development of ESCC are opium smoking, exposure to air pollutants, as well as the frequent consumption of hot beverages and a low intake of fruits and vegetables (Morgan et al. 2022b), and a high intake of red and processed meat (Nucci et al. 2021). These risk factors, were commonly observed in areas of high incidence of EC with the intake of hot beverages compounding the effects of smoking and alcohol intake (He et al. 2010).

Genetic Risks

Genomic-profiling of EAC has shown that this malignancy has an elevated mutational burden with one of the most mutated malignancy types (Alexandrov et al. 2013). Somatic mutation in TP53 was found in more than 83% of ESCC specimens (Song et al. 2014). Genetic mutations that regulate the cell cycle (CDKN2A, RB1, NFE2L2, CHEK1, and CHEK 2) and NOTCH 1 and NOTCH 3 mutations have been detected in 1–10% of ESCCs (D.-C. Lin et al. 2014a). Epidermal growth factor receptor (EGFR) was also found to be overexpressed in 59.76% of patients with ESCC and denotes a poor prognosis (Zhang et al. 2014). Single-nucleotide polymorphism DNA microarray has shown that 19% of patients with EAC demonstrate CCNE1 gene amplification. Raised levels of cyclin E were found in BE (5.8%), low-grade dysplasia (19.0%), high-grade dysplasia (35.7%), and EC (16.7%) (Zhou et al. 2014). The pathophysiology of esophageal cancer is depicted in Figure 1.

Esophageal Microbiome and Carcinogenesis

Dysbiosis in the Esophageal Adenocarcinoma cascade

The normal distal esophagus harbors a distinct microbiota that includes six major phyla: *Firmicutes*, *Bacteroides*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *TM7* (Pei et al. 2004). It also includes five major genera: *Streptococcus*, *Prevotella*, *Veillonella*, *Haemophilus, Neisseria* (Sharma et al. 2022). However, patients with gastroesophageal reflux disease (GERD) and Barret's esophagus (BE) have increased abundances of gram-negative bacteria such as *Prevotella*, *Neisseria*, *Campylobacter*,

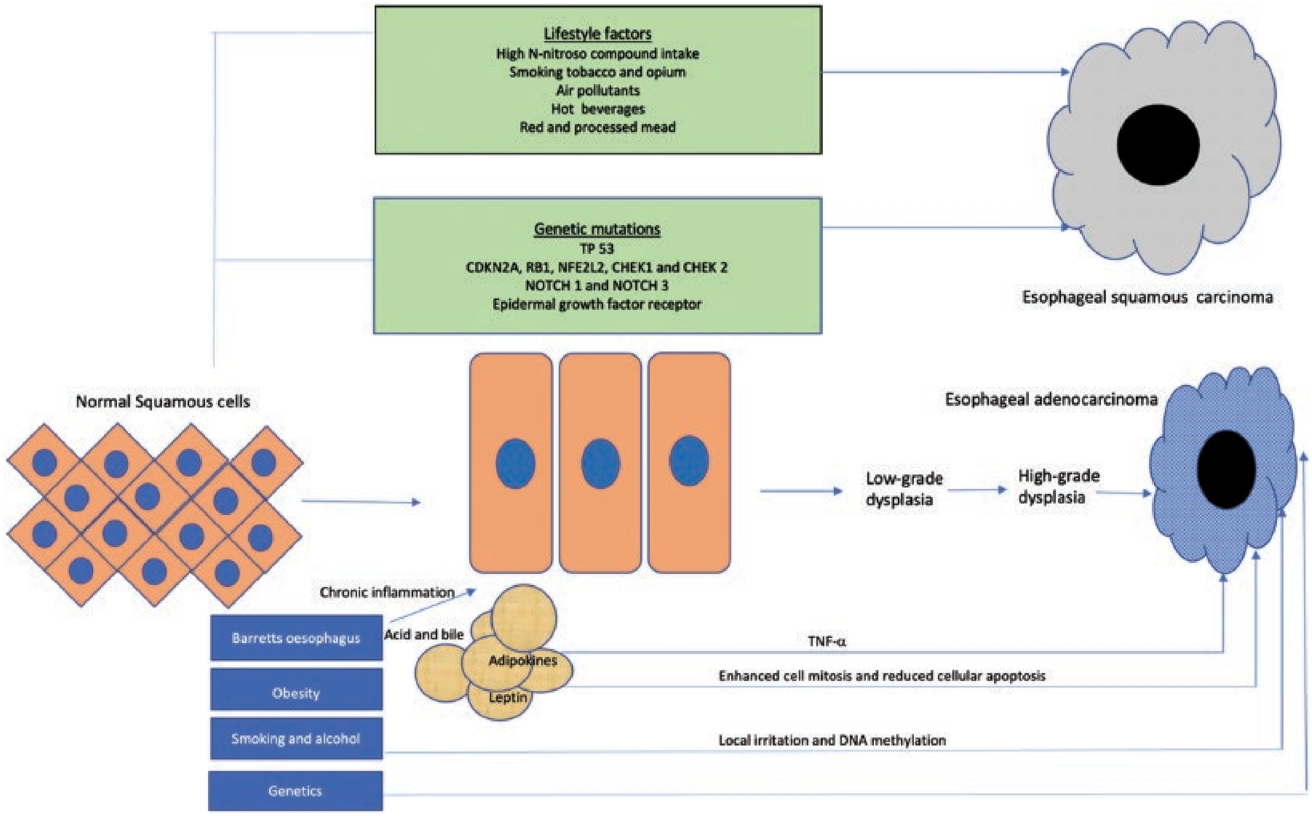
Lifestyle factors
High N-nitroso compound intake
Smoking tobacco and opium
Air pollutants
Hot beverages
Red and processed mead
Genetic mutations
TP 53
CDKN2A, RB1, NFE2L2, CHEK1 and CHEK 2
NOTCH 1 and NOTCH 3
Epidermal growth factor receptor
Esophageal squamous carcinoma
Normal Squamous cells
Esophageal adenocarcinoma
Low-grade dysplasia
High-grade dysplasia
Chronic inflammation
Acid and bile
Barretts oesophagus
Adipokines
Leptin
TNF-α
Obesity
Enhanced cell mitosis and reduced cellular apoptosis
Smoking and alcohol
Local irritation and DNA methylation
Genetics

Figure 1 Pathways of esophageal cancer.

Leptotrichia, and *Fusobacterium* and decreased abundance of gram-positive bacteria as compared to the normal esophagus (Blackett et al. 2013; Deshpande et al. 2018; Zhou et al. 2020).

The enrichment of gram-negative bacteria including *Campylobacter*, *Leptotrichia*, *Fusobacterium*, *Rothia*, and *Capnocytophaga* are comparable in the esophageal microbiome of GERD and BE patients. When comparing to the microbiome at the normal mucosa adjacent to the metaplastic tissue of BE, there is decreased abundance of *Prevotella*, *Selenomonas*, *Campylobacter*, and *Fusobacterium* decreased in the latter (Lopetuso et al. 2020). An increasing density of microbial networks were found along the progression of normal esophagus to GERD and BE (Deshpande et al. 2018). This suggests that bacteria become more dependent on each other to sustain their growth along the progression of the disease stages from GERD to BE.

Decreased microbial diversity was found in patients with esophageal adenocarcinoma (EAC) as compared to healthy individuals (Elliott et al. 2017; Snider et al. 2019). While Elliott et al. found that *Lactobacillus fermentum* and lactic acid bacteria were enriched in EAC, Snider et al. found that high grade dysplasia and EAC had increased abundance of *Enterobacteriaceae* and *Akkermansia muciniphila* and decreased abundance of *Veillonella* (Elliott et al. 2017; Snider et al. 2019). In contrast, a recent study showed that *Veillonella* and other bacterial genera including *Atopobium*, *Actinomyces*, *Ralstonia*, *Burkholderia*, and *Lautropia* progressively enriched along the GERD, BE and EAC sequence. These discrepancies of microbial composition in EAC may be caused by the low resolution of 16S rRNA sequencing which is only able to identify bacteria at genus level. It is possible that the species within the same genus may positively or negatively associate with EAC, thus resulting in apparent differences at the higher genus levels.

Apart from bacteria, presence of human papillomavirus (HPV) was more prevalent in dysplasia and EAC but not in BE as compared to healthy controls (Rajendra et al. 2013). The virus was mostly detected at the transformation zone (Rajendra et al. 2013). Moreover, the viral oncogene was highly associated with disease severity in dysplasia and EAC patients with viral positivity than those with viral negativity (Rajendra et al. 2013). This suggests that HPV may contribute to esophageal carcinogenesis.

Dysbiosis and EAC Carcinogenesis

Toll-like receptors (TLR), that recognize pathogen associated molecular patterns, have been suggested to interact with the esophageal microbiota. For example, TLR2 is expressed in the basal keratinocytes in normal squamous esophagus (Verbeek et al. 2016). However, its expression is around the papillae high up in the epithelium in reflux esophagitis (Verbeek et al. 2016). In BE, TLR2 is expressed mostly in superficial epithelial cells and deeper crypts, and in lamina propria as well (Verbeek et al. 2016). In EAC, TLR2 is highly expressed as compared to normal esophagus, reflux esophagitis and BE and its expression is diffuse throughout the biopsy (Verbeek et al. 2016). Interestingly, long term activation of TLR2 together with bile salts in BE epithelial cells (BAR-T) results in higher expression of mitochondrial and lysosomal enzymes and other factors regulating the endocytosis as compared to the cells exposed to bile salt only. Furthermore, TLR2 also heterodimerizes with TLR1 or TLR6 to recognize a wider range of microbial components. Consistent with this, the expression of TLR1 and TLR6 is also increased in BE and EAC (Huhta et al. 2016). This suggests that a wide range of bacteria from the dysbiotic esophageal microbiota may activate the TLR2 signaling pathway under stress conditions, leading to inflammation. This is supported by a recent study that TLR2 stimulation results in induction of pro-inflammatory cytokines, chemokines, and factors that activate the inflammasome in macrophages in BE organoid and early-stage EAC cell models (Flis et al. 2021). Whether this TLR2-mediated inflammation contributes to the EAC progression requires further investigation in *in vivo* models.

Apart from TLR2, TLR4 has been implicated in EAC carcinogenesis. The expression of TLR4 is increased in reflux esophagitis, BE and EAC as compared to the normal squamous esophagus (Verbeek et al. 2014). Inhibition of TLR4 activation by an inhibitory peptide or by TLR4 gene mutation reduces the expression of inflammatory markers including intercellular adhesion molecule-1 and IL-8, and the development of hyperplastic and proliferative response of the esophageal mucosa in the surgical reflux mouse model (Gergen et al. 2021). This suggests that TLR4 activation promotes inflammation in reflux esophagitis, and BE, leading to the progression of EAC. This TLR4 activation could have resulted from LPS, a bacterial cell wall component, present in the dysbiotic esophageal microbiota. LPS has been shown to induce NFkB activation and IL-8 secretion in the BE cell line (BAR-T) via TLR4 (Verbeek et al. 2014). It also induces IL-8 secretion and cyclooxygenase-2 (COX2) expression in *ex vivo* BE cultures (Verbeek et al. 2014). Consistent with this, increased COX2 expression is found in BE mucosa (Buttar et al. 2002) and COX2 inhibitor decreases esophageal inflammation and the risk of EAC development in a BE rat models (Buttar et al. 2002). Taken together, these studies suggest that LPS from the dysbiotic esophageal microbiota activates TLR4 signaling pathway and COX2 expression in the esophageal epithelium. This leads to chronic inflammation and the progression of EAC.

Epidemiology of Gastric Cancer

Global Burden and Time Trends

There has been a significant shift in the global epidemiology of gastric cancer (GC) (Sekiguchi et al. 2022). Gastric cancer demonstrated the second highest incidence and mortality worldwide in 1990, while in 2020 Gastric cancer has become the fifth commonest cancer and the fourth common cause of cancer death worldwide (Sung et al. 2021).

Approximately 1.1 million cases of GC (720,000 males and 370,000 females) were diagnosed globally in 2020 which resulted in 770,000 deaths (65% males) (Morgan et al. 2022a). The global age-standardized incidence decreased by 28.0% in 2017 compared to 1990 while the age-standardized mortality decreased by 48.7% with the most remarkable decrease noted in Japan and South Korea (Etemadi et al. 2020) due to the advancement in diagnosis and treatment (Rawla and Barsouk 2019). However, the decrease in GC was less pronounced in populations such as the US Caucasian population, Canada, Columbia, Denmark, Brazil, Germany, Israel, and India (Luo et al. 2017).

Human Development Index has been shown to correlate with the incidence of gastric cancer. It is estimated that 86% (885,119 of 1,033,701) of new GC cases in 2018 were diagnosed in areas with high as well as very high Human Development Index. Eastern Asia had the highest incidence rates of GC (32.1 per 100,000 men and 13.2 per 100,000 women), followed by Central and Eastern Europe which had 17.1 per 100,000 men and 7.5 per 100,000 women, and then South America which had 12.7 per 100,000 men and 6.9 per 100,000 women. North America had one of the lowest rates of GC (5.6 per 100,000 men and 2.8 per 100,000 women) followed by Africa (~5 per 100,000 men and 3–4 per 100,000 women) (Bray et al. 2018).

Gastric Cancer Survival Trends

The survival rate of gastric cancer is highly dependent upon the stage at diagnosis and also exhibits regional variability. The overall age-standardized five-year survival rate of GC was 31% in the United States (Rawla and Barsouk 2019) and 20.7% in the United Kingdom. Meanwhile, the overall age-standardized five-year survival in South Korea was reported to be 68.9% and 60.3% in Japan (Allemani et al. 2018). The overall 5-year survival has improved over time from. The survival rate for all patients diagnosed in 2000 was 18.8% and it increased to 28.0% in 2010. The survival rate for localized gastric cancer in 2000 was 46% and this increased to 60% for those diagnosed in 2010. Those with regional disease diagnosed in 2000 was 20% while this improved to 30% for those diagnosed in 2010. Unfortunately, the 5-year survival rate for patients diagnosed with distant disease remains dismal at less than 5%.

(Thrift & El-Serag, 2020). References: Thrift, A. P., & El-Serag, H. B. (2020). Burden of gastric cancer. Clinical Gastroenterology and Hepatology, 18(3), 534-542.

Risk Factors for Gastric Cancer

Gastric cancer consists of two main topographic types: Cardia gastric cancer (cancer arising at the area of the stomach next to the esophagogastric junction) and non-cardia gastric cancer (cancer arising from the distal region of the stomach) and can be divided histologically according to the Lauren classification into intestinal and diffuse. *Helicobacter pylori* infection is associated with histologic subtypes and accounts for approximately 89% of non-cardia gastric cancer cases worldwide (Plummer et al. 2015). The intestinal type is the most commonly found in the high gastric cancer incidence populations and is associated with the Correa cascade of inflammation (Correa et al. 1975).

Helicobacter Pylori Infection

It has been reported that an almost a staggering 50% of the world's inhabitants are currently infected with *Helicobacter pylori* (Fan et al. 2021). *Helicobacter pylori* is commonly found in the stomach antrum or body. Numerous elements such as adhesins, urease, flagella, and vacuolating cytotoxin (VacA) promote *Helicobacter pylori* activity and injury to the gastric cells (Gastli et al. 2021). *Helicobacter pylori* infection triggers chronic active gastritis, which, if persists, results in gastric glandular loss termed chronic atrophic gastritis. Atrophy begins in the incisura and, with time, progresses to the anterior and posterior gastric wall, where it is replaced by metaplastic cells. Metaplastic cells then transform into low-grade dysplastic cells, high-grade dysplastic cells, and subsequently, invasive carcinoma (Thrift and Nguyen 2021). On a molecular level, there is an increase in the activity of arginase which acts as a catalyst of L-arginine hydrolysis which results in the formation of ornithine and urea (Alam et al. 2018). Urea then forms ammonia which neutralizes gastric acid thereby promoting an alkaline pH which improves the survival of *Helicobacter pylori* allowing it to propagate (Wu et al. 2021). It has been shown that the Wnt/b-catenin pathway plays an important role in gastric epithelial cell regulation. *Helicobacter pylori* triggers abnormal Wnt/b-catenin pathway signaling via b catenin stabilization in gastric epithelial cells, which results in abnormal cellular proliferation which leads to carcinogenesis (X. Song et al. 2015b) (Song et al. 2015b).

The reduction in incidence and mortality of gastric cancer is due to the decrease in NGC (Rawla and Barsouk 2019), which is attributed to the improved diagnosis and treatment of *Helicobacter pylori*. Most *Helicobacter pylori* infection occurs in early childhood which is transmitted through the orofecal route (Sonnenberg 2013). Globally there has been a decrease in the prevalence of *Helicobacter pylori* infection (Sjomina et al. 2018). Africa (79.1%) had the highest prevalence of *Helicobacter pylori* infection followed by Latin American and the Caribbean (63.4%) and Asia (54.7%) while the lowest prevalence was seen in North America (37.1%) and Oceania (24.2%) (Hooi et al. 2017). A urban-rural disparity was seen in the prevalence of *Helicobacter pylori* infection whereby higher rates of infection were seen in the rural areas and correspondingly higher rates of gastric cancer were also observed (Wen et al. 2017). On the other hand, gastric cardia cancer incidence has been rising, particularly among developed countries (Clinton et al. 2020). This has been attributed to the increasing rates of smoking in developed countries. Data has shown that 11% of stomach malignancies worldwide and 17% of stomach malignancies in Europe are imputed to smoking (Clinton et al. 2020).

Smoking

Tobacco smoking has been linked with a variety of malignancies including gastric cancer. The Stomach Cancer Pooling Project (StoP) has shown that active smokers had a 25% greater risk of developing gastric cancer than never-smokers (OR, 1.25; 95% CI, 1.11–1.40). There was a linear relationship between cigarettes per day ($P<0.01$) and duration of smoking ($P<0.01$) with an OR od 1.33 (95% CI: 1.14 – 1,54). For 40 years of smoking and above, the risk was seen to be more marked for cardia than non-cardia gastric cancer (Praud et al. 2018). Quitting smoking was associated with a reduced rate of GC. The risk of GC of former smokers who quit more than ten years of tobacco became similar to that of never smokers (Praud et al. 2018).

Carcinogens found in tobacco such as the N-nitroso compound are pivotal to its carcinogenesis. In vitro studies have shown that tobacco smoke has a direct carcinogenic effect in the gastric mucosa. (Tayler and Piper 1977) In endoscopic studies, Tobacco smoking was demonstrated to promote dysplasia of gastric epithelium, chronic atrophic gastritis, and intestinal metaplasia (Kneller et al. 1992). Molecular mechanisms by which tobacco smoking promotes GC may be mediated via the polymorphism in the *GSTT1, SULT1A1, CYP1a1*, and *NAT2* genes which increase susceptibility to GC (Boccia et al. 2007). Smoking also has a compounding effect on the increased risk of susceptibility and persistence of *Helicobacter pylori* infection. Smoking also results in a lower efficacy of antibiotic eradication of *Helicobacter pylori* (Ferro et al. 2019).

Obesity and Lifestyle Factors

Obesity has also been shown to be associated with a modestly increased risk for cardia gastric cancer (X.-J. Lin et al. 2014a). Dietary factors that increase GC risk include a high salt diet (Morais et al. 2022) processed meat (Kim et al. 2019) nitrates (P. Song et al. 2015b). Excessive processed meat intake increased the risk for non-cardia GC but not cardia GC. Salt has been postulated to cause gastric mucosal damage and hypergastrinemia (Furihata et al. 1996) leading to chronic inflammation promoting *H. pylori* infection. Salt also potentiates the carcinogenicity of nitrates by enhancing its penetration. (Eusebi et al. 2020) Heavy alcohol consumption which is defined as more than five drinks per day increased the risk of gastric cancer (OR 3.13, 95% CI 1.15–8-64) (Laszkowska et al. 2021). A meta-analysis by Han et al. showed high total dietary fat intake more than 20 g/day correlated with an increased risk for GC (Han et al. 2015).

Genetic Risk

Hereditary cancer syndromes such as hereditary diffuse gastric cancer (HDCC), Lynch, hereditary breast and ovarian cancer (BRCA), Li-Fraumeni, familial adenomatous polyposis, and Peutz-Jeghers syndromes result in an increased risk for gastric cancer. Persons with HDCC syndrome have a 80% risk of developing GC (Hansford et al. 2015), While GC is usually sporadic, approximately 10% of GC cases have familial aggregation (Pocurull et al. 2021). HDCC is characterized by E-cadherin (CDH1) mutation results in an increased risk of early-onset diffuse gastric cancer and lobular breast cancer. HDCC is inherited in an autosomal dominant manner. The cumulative risk for gastric cancer in those with CDH1 mutations is 70% by 89 years for men and 56% for women (Hansford et al. 2015). It is recommended that any patient with two or more family members with a history of gastric cancer, irrespective of age with at least one diagnosed with gastric cancer, or anyone with a family member with diffuse gastric cancer at any age and lobular breast cancer diagnosed before the age of 70, a family history of two or more relatives with breast cancer diagnosed less than 50 years of age undergo CDH1 testing. Meanwhile, any patients who have been diagnosed with diffuse gastric cancer below the age of 50, have diffuse gastric cancer at any age who are of Maori ethnicity, have diffuse gastric cancer with a history or family history of cleft lip palate, a history of bilateral lobular breast cancer diagnosed before 70, or gastric cancer *in situ* signet ring or pagetoid spread of signet ring diagnosed less than 50 years of age undergo CDH1 testing (Blair et al. 2020).

Li-Fraumeni syndrome is an infrequently encountered hereditary cancer syndrome which is a result of TP53 germline mutation and is inherited in an autosomal dominant manner (Masciari et al. 2011). It is also associated with an increased risk of sarcoma, brain tumors, breast and adrenal cortical carcinomas, and breast cancer (Garber et al. 1991). Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary colorectal cancer syndrome that has a prevalence of 1 in 10,000 (Plawski et al. 2013). FAP is due to a mutation in the adenomatous polyposis coli (APC) gene. The endoscopic features of patients with FAP is multiple polyposis of the stomach. There is an increased prevalence of gastric adenomas, fundic gland polyps, and polyps with high grade dysplasia in these patients. There is a high rate of duodenal adenomas in patients with FAO reaching approximately 88 to 98% with the risk of duodenal malignancy as high as 18% by the age of 75. The risk of gastric adenocarcinoma is 1.3% in patients with FAP. Polyposis usually begins around puberty therefore it is recommended that colonoscopy screening begin at the age of 12 in patients with an affected family member (Bülow et al. 2012), hence it is recommended by international guidelines that screening esophagealgastroduodenoscopy (EGDS) should commence at age 25 (Monahan et al. 2020; van Leerdam et al. 2019; Yang et al. 2020).

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited genetic disorder that results in the development of mucocutaneous pigmentation and multiple hamartomatous polyps in the gastrointestinal tract. It is due to a mutation in the STK11 gene which is located in 19p 13.3 (Aretz et al. 2005). STK11 is a tumor suppressor gene that is responsible for cell cycle and cell proliferation pathways that regulate apoptosis and RAS-related cell transformation (Karuman et al. 2001). The development of GI malignancies in PJS occurs through the hamartoma-adenoma-carcinoma pathway. (Bosman 1999) PJS has an incidence of approximately 1 in 250,000 and carries a 15 to 18-fold increased risk of cancer compared to the general population (Kalloo and Shanahan 2016). A clinical diagnosis of PJS can be made when one of the criteria is met: two or more pathologically ascertained Peutz-Jeghers polyps, detection of Peutz-Jeghers polyps and family history of Peutz-Jeghers in a close relative, characteristic mucocutaneous pigmentation in the mouth, lips, nose, eyes, genitalia, or fingers with a family history of PJS, any Peutz-Jeghers polyps in a patient with a characteristic mucocutaneous pigmentation (Beggs et al. 2010). In view of the increased risk of malignancy, it is advocated that a screening EGDS be performed at eight years of age in those with PJS. If polyps are found, polypectomy should be performed and EGDs should be repeated in one to three-year intervals. If no polyps are found at baseline screening EGDs therefore the next EGD can be performed at 18 years of age (Monahan et al. 2020; van Leerdam et al. 2019).

Other Risk Factors for Gastric Cancer

Other less common risk factors for GC include Epstein-Barr virus infection, Menetrier’s disease, and autoimmune gastritis. Epstein Barr Virus was found in approximately 8% of gastric cancers; however, there is inadequate evidence for a direct causal relationship for Epstein Barr Virus in gastric carcinogenesis (Group 2012). Menetrier’s disease is a condition where hypertrophic gastropathy develops in the body of the stomach resulting in the formation of giant gastric folds, protein-losing enteropathy, and achlorhydria. Histologically, there is presence of massive foveolar hyperplasia (Toubia and Schubert 2008). Smoking increased the risk of development of Menetrier’s disease however alcohol use and *Helicobacter Pylori* did not increase this risk. The risk of GC was 8.9% after 10 years of the diagnosis of Menetrier’s disease and the survival was 72.7% at 5 years and 65% at 10 years (Almazar et al. 2021).

Autoimmune gastritis accounts for under 5% of chronic gastritis cases (Lahner et al. 2015). It is the result of autoimmune T-cell mediated destruction of the oxyntic mucosa of the proximal stomach which is mediated by autoantibodies against the parietal cells and intrinsic factor (Zhang et al. 2013). This results in the development of atrophy of the oxyntic gastric mucosa with hypo- or achlorhydria. Complications of B12 malabsorption (Pernicious anemia) and iron deficiency anemia ensue (Coati et al. 2015). Pernicious anemia carries approximately seven-fold higher risk of gastric malignancy (Weise et al. 2020). It is important to note that the hypo- or achlorhydria gives rise to hypergastrinemia and enterochromaffin-like cell hyperplasia which can develop into a neuroendocrine tumor (Bordi et al. 1995). The prevalence of enterochromaffin-like cell neuroendocrine tumors in autoimmune gastritis is markedly elevated compared to *Helicobacter pylori* gastritis (Waldum and Fossmark 2019). The pathophysiology of gastric cancer is depicted in Figure 2.

Factors Protective of Gastric Cancer

The Mediterranean diet which incorporates vegetables, legumes, whole grains, fish, and olive oil which are high in polyunsaturated fat and low in saturated fats and nitrites have been shown to be protective against GC in those with high adherence (Álvarez-Álvarez et al. 2021). The Stomach cancer Pooling (STOP) a global epidemiological study on GC demonstrated that there was a marked decrease in GC risk in those with highest tertile consumption of fruits (0.76, CI 0.64–0.90), vegetables (OR 0.68, CI 0.56–0.84) and fruits and vegetables combined (OR 0.61, CI 0.49–0.75) compared to those in the lowest tertile (Ferro et al. 2020). Other beneficial food include whole grains and nuts (Zhang et al. 2020), Vitamin D levels above 20 ng/ml (Kwak and Paik 2020), and ascorbic acid and polyphenols found in fruits and vegetables was found to lower the risk of GC (Toh and Wilson 2020).

Microbiome and Gastric Cancer

Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes are the major phyla present in the healthy gastric mucus layer (Fakharian et al. 2022). *Prevotella, Veillonella, Streptococcus, Neisseria, Fusobacterium*, and *Haemophilus* are the main genera present in the healthy gastric microbiota, but their abundance varies among human individuals from different geolocations (Fakharian et al. 2022). In general, the overall microbial load of the stomach is around 10^2–10^4 CFU/ml which is lower than that of the colonic microbiota (10^{10}–10^{12} CFU/ml) owing to the acidic environment that limits microbial colonization (J. Yang et al. 2021b).

Helicobacter pylori (*H. pylori*) plays a major role in the progression from atrophic gastritis to intestinal metaplasia to gastric cancer (GC) (Stewart et al. 2020). Chronic *H. pylori* infection induces chronic gastric inflammation, leading to atrophic gastritis (Goldenring and Mills 2022). These effects are mediated by multiple virulence factors of *H. pylori*. Of these, VacA increases the mitochondrial membrane permeability, impairs endocytosis trafficking, and triggers apoptosis in gastric epithelial cells (Gauthier et al. 2005; Matsumoto et al. 2011; Willhite and Blanke 2004). It also

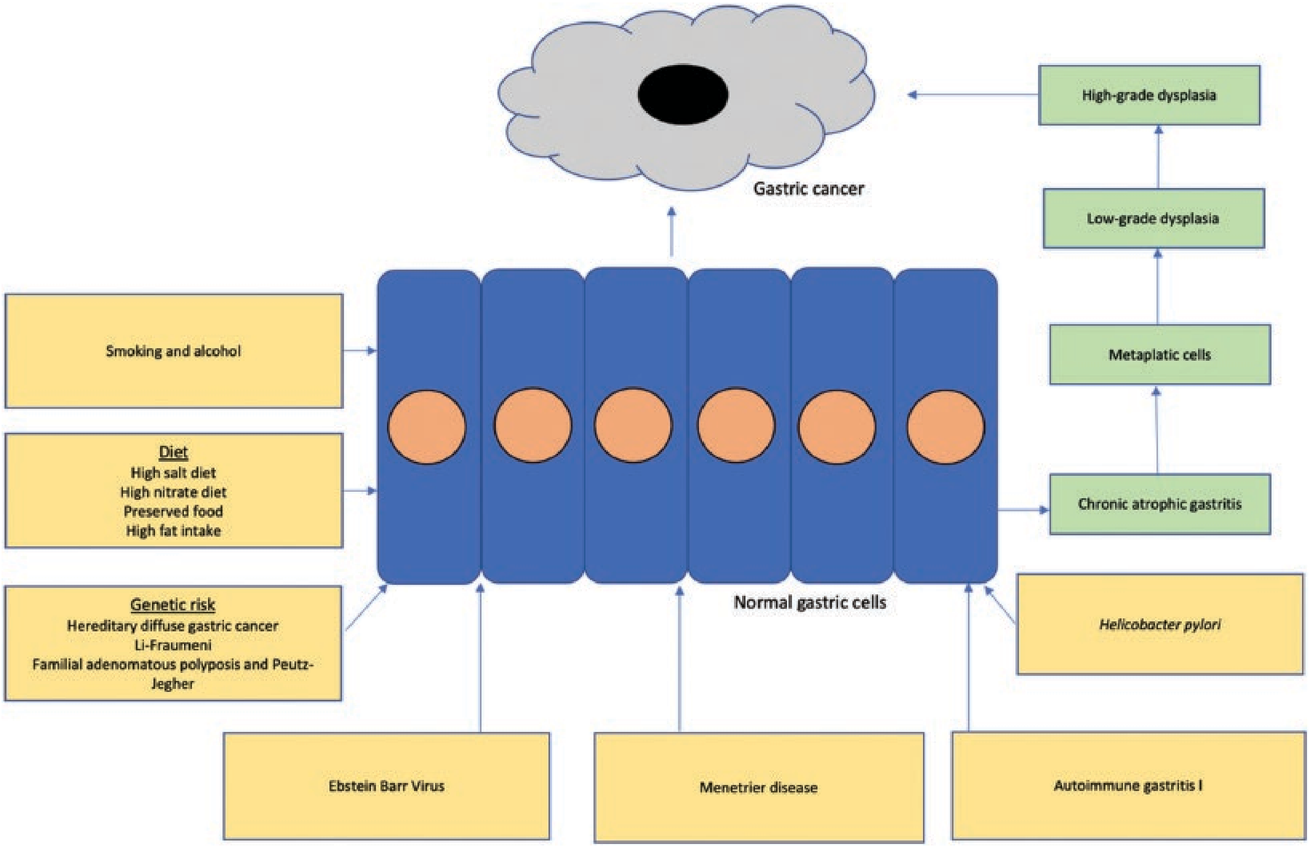
Gastric cancer
High-grade dysplasia
Low-grade dysplasia
Metaplatic cells
Chronic atrophic gastritis
Smoking and alcohol
Diet
High salt diet
High nitrate diet
Preserved food
High fat intake
Genetic risk
Hereditary diffuse gastric cancer
Li-Fraumeni
Familial adenomatous polyposis and Peutz-Jegher
Normal gastric cells
Helicobacter pylori
Ebstein Barr Virus
Menetrier disease
Autoimmune gastritis I

Figure 2 Pathways of gastric cancer.

stimulates mast cells to produce pro-inflammatory cytokines such as IL-6 and TNF-a (Supajatura et al. 2002), leading to the *H. pylori*-associated gastritis. Furthermore, VacA, g-glutamyl transpeptidase and bacterial cholesterol of *H. pylori* induce T_H17 immune responses, contributing to the development of gastritis. On the other hand, CagA and T4SS form a complex that deliver CagA to the infected host cells across the outer and inner bacterial membranes (Chung et al. 2019; Knorr et al. 2019). CagA then induces inflammatory responses and proliferation, inhibits apoptosis, impairs cell-cell junctions, and leads to loss of cell polarity in the gastric epithelial cells, thus promoting gastric carcinogenesis (Bagnoli et al. 2005; Buti et al. 2020, 2011; Yang et al. 2018). This chronic inflammation induced by *H. pylori* virulence factors enhances the production of reactive oxygen species and reactive nitrogen species which damage DNA (Shimizu et al. 2017). *H. pylori* also induces DNA damage via direct adhesion of live bacteria with the host cells and impairs the DNA repair system via the host long noncoding RNAs, SNHG17 (Toller et al. 2011). The DNA damage results in genomic instability and accumulation of mutations, leading to gastric carcinogenesis.

The chronic gastric inflammation results in the death of hydrochloric acid secreting parietal cells. The hypochlorhydria allows the gastric colonization and outgrowth of oral and lower bowel microbes that are not normally present in the acidic condition of the stomach, leading to dysbiosis of the gastric microbiota. The enriched oral bacteria in the mucosa of GC includes *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes* (Coker et al. 2018; Liu et al. 2022). This enrichment only occurs in GC but not in other early stages including superficial gastritis, atrophic gastritis, and intestinal metaplasia (Coker et al. 2018). In addition, *H. pylori* reduces microbial diversity, changes the microbiota composition, and weakens the interactions among gastric microbes (Liu et al. 2022). The first link between gastric dysbiosis and carcinogenesis was demonstrated by Lee et al., using the INS-GAS transgenic mouse model for gastritis with achlorhydria (Lee et al. 2008). Lee et al. treated the INS-GAS transgenic mice with three antibiotics including metronidazole, omeprazole, and clarithromycin prior to *H. pylori* infection (Lee et al. 2008). Killing of *H. pylori* by the antibiotics lowers the severity of gastric dysplasia several weeks post-infection (Lee et al.

2008). Intriguingly, INS-GAS transgenic mice treated with the antibiotics and without *H. pylori* infection also have a reduced severity of dysplasia (Lee et al. 2008). These data suggest that antibiotics not only eradicate *H. pylori* but also the gastric microbiota, protecting the mice from gastric carcinogenesis. This idea is further supported by two later studies. Lofgren et al. demonstrated that germ-free INS-GAS mice have a delayed development of gastric lesions as compared to INS-GAS mice with a more complex microbiota and *H. pylori* infection (Lofgren et al. 2011). Lertpiriyapong et al. further examined if a diverse gastric microbiota is required for the development of gastric lesions (Lertpiriyapong et al. 2014). The risk for gastric cancer development was compared among three groups of INS-GAS mice that were germ-free, had restricted microbiota (only containing *Lactobacillus, Clostridium, Bacteroides*), and had complex microbiota (Lertpiriyapong et al. 2014). They found that the rate of gastric cancer development is similar in mice with a restricted and complex microbiota (Lertpiriyapong et al. 2014). However, mice with a restricted microbiota have enhanced gastric inflammation, epithelial defects, oxyntic gland atrophy, epithelial hyperplasia, and dysplasia as compared to the germ-free mice (Lertpiriyapong et al. 2014). Taken together, these results suggest that *H. pylori* acts synergistically with the bacterial community for potentiating gastric neoplasia development.

Despite the above evidence, it remains unknown if gastric dysbiosis in humans is sufficient to induce gastric carcinogenesis. A recent study addressed this research question by transplanting the microbiota obtained from chronic superficial gastritis, intestinal metaplasia, or GC into germ-free wild type mice (Kwon et al. 2022). They found that the gastric microbiota from patients with intestinal metaplasia or GC colonized the mouse stomachs and induced premalignant lesions including loss of parietal cells, increased inflammation, and enhanced gastric cell proliferation (Kwon et al. 2022). These mice also developed gastric dysplasia after one year of transplantation (Kwon et al. 2022). These results suggest that the gastric dysbiotic microbiota from intestinal metaplasia and GC but not gastritis is sufficient to induce gastric carcinogenesis. They also explain why more than 50% of the world population are infected with *H. pylori* but only 1–3% of these infected individuals develop gastric cancer (Stewart et al. 2020). It is possible that *H. pylori* induces chronic gastritis and hypochlorhydria, providing a favorable environment for the development of gastric dysbiosis which in turn potentiates the gastric carcinogenesis with or without the synergistically carcinogenic effect by *H. pylori*. Further investigation is required to understand the molecular mechanism on how this gastric dysbiotic microbiota promote gastric carcinogenesis and to examine if this gastric dysbiosis could be treated to prevent gastric cancer.

Epidemiology of Colorectal Cancer

Global Burden and Time Trends of Colorectal Cancer

Colorectal cancer is ranked third in worldwide incidence of malignancies in 2020 with 1.9 million new cases diagnosed and accounted for 935,000 cancer-related deaths making it the second deadliest malignancy (Sung et al. 2021). The crude incidence rate was 24.8 per 100,000 and the age-adjusted incidence rate was 19.5 per 100,000 while the crude mortality rate was 12 per 100,000 and the age-standardized mortality rate was 9 per 100,000 (Sung et al. 2021). There is significant geographic variability in CRC incidence and a correlation with the human development index (HDI). The incidence and mortality of CRC in the past two decades in developed countries with high HDI has decreased largely due to established CRC screening programs and polypectomy (Kanth and Inadomi 2021). There has been an increase in the incidence of CRC in Eastern Europe, South America, and South Eastern and South Central Asia which is possibly associated with an affluent lifestyle encompassing higher animal-source food, higher calorie intake, reduced physical activity, and increased obesity (Sung et al. 2021). The highest age-standardized incidence rate was reported in Australasia at 48.3 per 100,000 population, while the lowest was seen in central sub-Saharan Africa at 7.7% per 100,000 (Collaborators 2022). Central Europe has the highest age-standardized mortality rate (23.6 per 100,000). On the other hand, South Asia had the lowest figure for age-standardized mortality rate (7.3 per 100,000) (Collaborators 2022).

Early-onset Colorectal Cancer

Early-onset CRC is defined as CRC occurring before the age of 50. The average age of diagnosis of CRC is 68 years of age in men and 72 years of age in women (Sung et al. 2021). However, there has been a steady increase in the incidence of early-onset CRC and a decrease in late-onset CRC. There has been a rise in early-onset CRC in the last three decades. In the United States there has been an increase of 45% of CRC in adults aged 20 to 49 years from 1992 (8.6 per 100,000) to 2016 (13.1 per 100,000) (Stoffel and Murphy 2020). There has also been an increasing trend of early CRC across Europe. CRC in ages 20 to 29 increased from 0.8 in 1990 to 2.3 per 100,000 in 2016 while in ages 30 to 39 there was an increase from 2.8 in 2006 to 6.4 per 100,000 in 2016 and in ages 40 to 49 an increase from 15.5 in 2005 to 19.2 per 100,000 in 2016 was observed (Vuik et al. 2019). A similar trend was seen in Australia and New Zealand (Siegel et al. 2019) as well as in industrialized Asian countries such as Japan, Hong Kong, South Korea, and Taiwan (Sung et al. 2021). Early onset CRC mortality has also been on the rise with an increase of 1.3% per year from 2008 and 2017 (Siegel et al. 2019). Decreasing colorectal cancer trends were noted in three developed countries: Italy, Austria, and Lithuania. Of note Austria implemented an earlier CRC screening age commencing at 40 years of age which likely contributes to this trend (Vuik et al. 2019).

In terms of clinical presentation, early-onset CRC usually presents symptomatically in 70 to 95% of cases (Silva et al. 2019) whereas late onset CRC patients are usually diagnosed fortuitously likely during CRC screening colonoscopy (F. W. Chen et al. 2017b). Patients with early onset CRC also report a longer duration of symptoms and have a lengthier delay in diagnosis and are diagnosed at a more advanced stage compared with late-onset CRC (F. W. Chen et al. 2017b). Early onset CRC had a higher frequency of left-sided disease with more aggressive histology with approximately 27.9% having poorly or undifferentiated cancer (F. W. Chen et al. 2017b). Insights into the adenoma-carcinoma pathway have revealed that the most effective way to prevent sporadic CRC is by the removal of colorectal adenomas. According to a 20-year prediction model reported based on Cancer Tomorrow on Global Cancer Observatory (https://gco.iarc.fr), there would be 1.93 million instances of colon, rectal, and anal cancers globally in 2020, and 3.15 million in 2040 (Xi and Xu 2021). This is based on projected aging, population growth, and human advancement. The surge was ascribed to a shift in lifestyle and nutrition toward a more westernized norm (Xi and Xu 2021).

Risk Factors of Colorectal Cancer

Polyps, the Adenoma-carcinoma Sequence and the Risk of Colorectal Cancer

Colorectal cancer is divided into sporadic, colitis-associated, and hereditary colorectal cancer all of which undergo different carcinogenic pathways. It is estimated that 60 to 65% of CRC are sporadic, while 25% have a family history but no genetic cancer syndrome whereas only 5% are hereditary (Keum and Giovannucci 2019; Migliore et al. 2011). The development of CRC undergoes four key phases which encompass initiation, promotion, progression, and metastasis. The process of initiation begins with an irreparable genetic injury that results in neoplastic transformation. The promotion stage ensues when the neoplastic cells proliferate resulting in neoplastic growth. Thereafter the progression phase occurs. Genetic and epigenetic remodeling causes the cells to have a selective growth advantage which results in their metastatic ability. Metastasis then occurs via the bloodstream or lymphatic system (Keum and Giovannucci 2019).

Most CRCs begin with a polyp. There are two major subtypes of polyps: adenomatous (adenomas) and serrated polyps. Approximately 85 to 90% of CRCs arise from adenomas (Conteduca et al. 2013). However, below 10% of adenomas develop into CRC (Conteduca et al. 2013). Adenomas with characteristics of villous histology, high-grade dysplasia, or size being more than 1 cm have been termed high-grade adenomas and possess a greater likelihood of progression to malignancy (30–50%) compared with non-advanced adenomas (1%) (Conteduca et al. 2013). An adenoma develops from mutations in *APC*, the tumor suppressor gene. This results in the overactivation of the Wnt/b-catenin signaling pathway and progresses to dysregulated cell proliferation forming an adenoma (Dow et al. 2015). Thereafter, *KRAS* mutations enhances the adenoma proliferation, and subsequent inactivation of TP53 tumor suppressor gene results in the development of CRC (Armaghany et al. 2012).

Another group of polyps, the serrated polyps encompass traditional serrated adenomas, sessile serrated adenomas, and hyperplastic polyps. The hyperplastic polyp (HP) is the predominant variant that was previously believed to be completely benign, however, recent data have shown that large polyps and/or in the proximal colon may progress to CRC via the serrated pathway (East et al. 2017). An estimated 10–15% of sporadic CRC arise from serrated polyps (Conteduca et al. 2013). One of the critical events in this pathway is mutation of the *BRAF* oncogene which activates the MAPK pathway and results in the development of hyperplastic polyp. Progression to sessile serrated adenoma is propagated by CIMP (Kedrin and Gala 2015). The risk of progression can be halted by removing these adenomas via polypectomy during a colonoscopy thus reducing the CRC risk.

Inflammatory Bowel Disease

Chronic inflammation results in a different carcinogenic pathway. In chronic inflammation, *TP53* mutation occurs early and low-grade dysplasia arises from chronic inflammation and usually occurs in flat mucosa and has an accelerated pathway to high-grade dysplasia and finally CRC (Itzkowitz and Yio 2004). Due to the fact that these lesions occur in flat mucosa, their detection is challenging hence chromoendoscopy or high-definition endoscopy is superior to white light imaging for dysplasia surveillance (Buchner and Lichtenstein 2016).

Risk Factors for Early-onset Colorectal Cancer

Early-onset CRC has been on the rise in highly Westernized countries. Early-onset CRC is genetically, pathologically, and molecularly diverse (Pearlman et al. 2017). An estimated 30% of early-onset CRC patients have a family history of CRC or one first-degree relative with CRC and out of that only 13% had a germline mutation (Pearlman et al. 2017). Early-onset CRC has been found to be MSI-high in 10–30% of the cases of CRC compared with ~15% of overall CRCs (Conteduca et al. 2013). The obesity epidemic among young children and adolescents parallels the rise in early-onset CRC (Keum and Giovannucci 2019). It has been shown that women with a BMI of 23 or above at the age of 18 had almost 60% increased risk of early-onset CRC compared with women who had a BMI <23. Thus early-onset CRC is multifactorial and personalized screening should be adopted in those aged 45 years and younger (X.-J. Lin et al. 2014a).

Hereditary Colorectal Cancer Syndrome Risk Factors

High penetrance syndromes contribute 2–5% of all CRC cases. These include Lynch syndrome caused by dysfunction of the mismatch repair system, familial nonpolyposis coli (FAP) caused by *APC* mutations, and hereditary nonpolyposis coli (HNPCC) due to mutations of mismatch repair (MMR) genes (Kory 2010). HNPCC is a genetic disease with autosomal dominant inheritance and accounts for 2–4% of CRC (Kory 2010). It arises as a result of mutations in the DNA mismatch repair gene (MMR) encompassing MLH1, MSH2, MSH6, and PMS2 (Markowitz and Bertagnolli 2009). HNPCC affects approximately 1 in 300 individuals in the West (Win et al. 2017) and is complicated by MSI-high CRC primarily in the proximal colon (Lynch and De la Chapelle 2003) which starts with the occurrence of a few polyps which undergo an accelerated carcinoma sequence and progress to CRC within 2 to 3 years in contrast to 8 to 10 years in the general population (Jass et al. 1994). There is a 60% lifetime risk of development of CRC in HNPCC (Winawer et al. 1997), however it only accounts for <1% of CRC (Patel and Ahnen 2012). It is recommended that patients who have MLH1 and MSH2 mutations undergo screening colonoscopy starting at the age of 25 and subsequently yearly until the age of 75. Meanwhile, patients with MSH6 and PMS2 mutations should undergo a screening colonoscopy starting at the age of 35 and subsequently 2-yearly until the age of 75 (Monahan et al. 2020; van Leerdam et al. 2019).

Familial adenomatous polyposis (FAP) is a result of an inherited germline *APC* mutation (Patel and Ahnen 2012). It has a prevalence of 1 in 10,000 and results in approximately 2 to 5% CRC (Kory 2010). The risk of CRC is almost 100% by the age of 40 without prophylactic panproctocolectomy (Winawer et al. 1997). APC plays a role as tumor suppressor gene of the Wnt/β-catenin signaling pathway via APC/AXIN/GSK3 β-catenin inactivation (X. Yang et al. 2021b). Mutations in APC are characterized by the stabilization of β-catenin, entry of β-catenin into the nucleus, and a surge in cellular proliferation (Stefanski and Prosperi 2020). Phenotypically, this is expressed by the development of 100 polyps and above throughout the colon which starts in puberty (Patel and Ahnen 2012). Polyps also develop in the duodenum in nearly all patients (88 to 98%) and eventually two thirds of patients develop duodenal adenomas (Burke et al. 1999). The risk of developing duodenal malignancy is 4% by the age of 70 (Kanth et al. 2017) and the risk of ampullary malignancy is 18% by 75 years of age (Björk et al. 2001). In view of the elevated risk of CRC in those with FAP, screening colonoscopy is recommended to commence at 12 to 14 years and every 1 to 2 years thereafter (Monahan et al. 2020; van Leerdam et al. 2019). Colonoscopy surveillance for FAP has been shown to reduce the incidence of CRC. FAP patients who were under surveillance colonoscopy had a CRC incidence of 3.8 to 9.4% compared to those presenting symptomatically at 33.6 to 66.2%. There was also a mean delay in the occurrence of CRC by up to 16 years with a better survival of up to 12 years (Barrow et al. 2013).

Peutz-Jeghers syndrome (PJS) is due to a mutation in the serine threonine kinase 11 tumor suppressor gene (STK11/LKB1 gene) and is inherited in an autosomal dominant manner. This is manifested by the formation of gastrointestinal tract polyposis which occurs most often in the small bowel (60 to 90%) in particular the jejunum (Latchford et al. 2011). Complications of this include anemia, bleeding and bowel intussusception (Latchford et al. 2011). The cumulative risk of colorectal malignancy was 39% at 15 to 64 years of age (H.-Y. Chen et al. 2017b). It is recommended that patients with PJS undergo a baseline colonoscopy at eight years of age in subjects who are asymptomatic with subsequent surveillance intervals ranging from one to three years depending on the colonoscopic findings (van Leerdam et al. 2019).

Lifestyle and Dietary Factors

Obesity is a state of low-grade chronic inflammation which results in the release of pro-inflammatory cytokines by adipokines that mediate tumorigenesis. There has been evidence to suggest that waist circumference is a greater risk factor than BMI for CRC (Song et al. 2016). This was due to the secretion of proinflammatory adipokines, which resulted in chronic low-grade inflammation (Ouchi et al. 2011) as well as the presence of insulin resistance which creates an optimal condition for tumor development (Ouchi et al. 2011). Insulin resistance also gives rise to hyperinsulinemia which increases free insulin-like growth factor 1 (IGF-1) which promotes CRC via enhanced cell proliferation and reducing apoptosis (Calle and Kaaks 2004).

A sedentary lifestyle has been shown to be a risk factor for CRC (de Rezende et al. 2018). The American Cancer Society has recommended that adults should engage in 150–300 min of moderate-intensity physical activity per week, or 75–150 min of vigorous-intensity physical activity, or an equivalent combination, while achieving or exceeding the upper limit of 300 min is optimal (Rock et al. 2020). Alcohol is also a risk factor for CRC, whereby drinking more than 1 alcoholic drink per day was shown to increase the CRC risk (RR 1.04, 95% CI 1.01–1.06) compared to non or infrequent consumption of alcohol (Choi et al. 2018). Alcohol goes to the colonocytes via systemic circulation and is metabolized by alcohol dehydrogenase into acetaldehyde (Salaspuro 1997) which injures the mucosa causing regenerative cellular proliferation

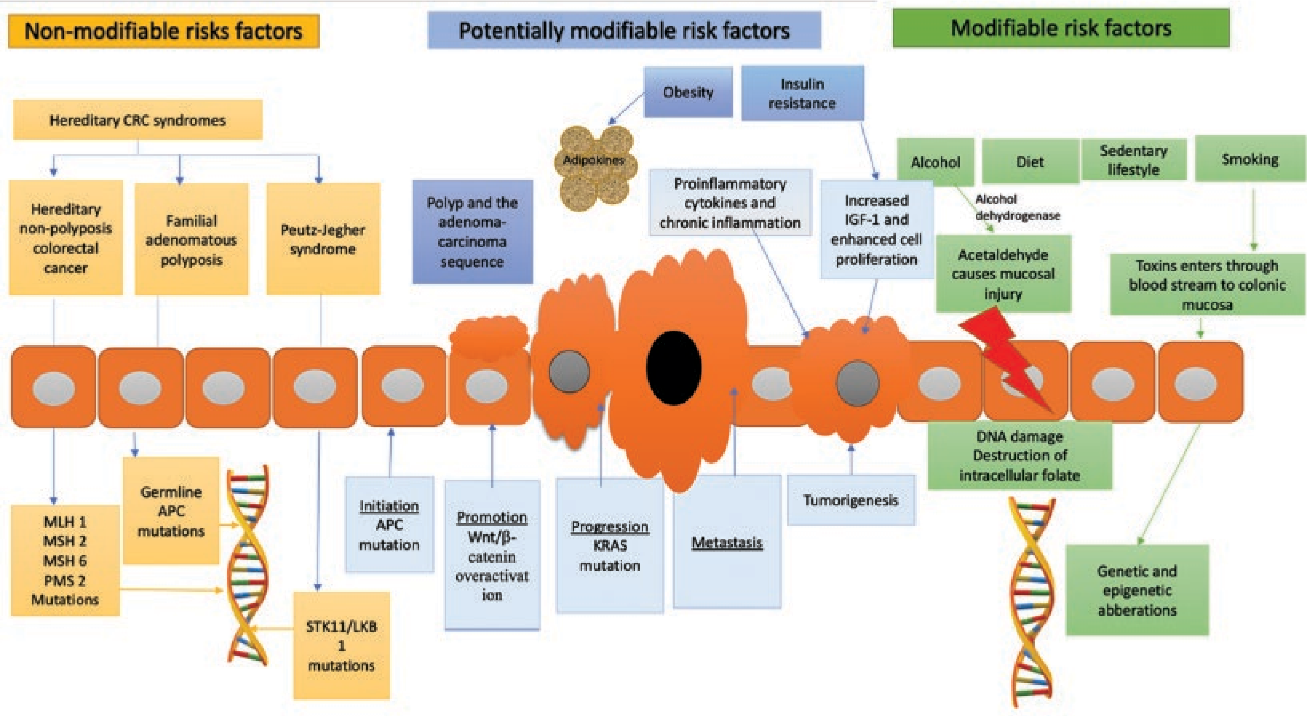
Non-modifiable risks factors
Potentially modifiable risk factors
Modifiable risk factors
Hereditary CRC syndromes
Hereditary non-polyposis colorectal cancer
Familial adenomatous polyposis
Peutz-Jegher syndrome
Polyp and the adenoma-carcinoma sequence
Obesity
Insulin resistance
Adipokines
Proinflammatory cytokines and chronic inflammation
Increased IGF-1 and enhanced cell proliferation
Alcohol
Diet
Sedentary lifestyle
Smoking
Alcohol dehydrogenase
Acetaldehyde causes mucosal injury
Toxins enters through blood stream to colonic mucosa
MLH 1
MSH 2
MSH 6
PMS 2
Mutations
Germline APC mutations
STK11/LKB 1 mutations
Initiation APC mutation
Promotion Wnt/β-catenin overactivation
Progression KRAS mutation
Metastasis
Tumorigenesis
DNA damage Destruction of intracellular folate
Genetic and epigenetic abberations

Figure 3 Pathways of colorectal carcinogenesis.

(Seitz and Stickel 2007). Intracellular acetaldehyde causes DNA damage and destroys intracellular folate which is needed for DNA production and methylation (Giovannucci and Martinez 1996; Seitz and Stickel 2007).

Smoking is another established risk factor for CRC, the risk of CRC has been found to correspond with the number of pack years, the RR for five pack years: 1.06 95% CI 1.03 – 1.08, the RR for 30 pack years 1.26, 95% CI 1.17–1.36. Smoking exerts its effects through genetic and epigenetic aberrations (Giovannucci and Martinez 1996). Other risk factors for CRC include high processed meat, low fiber, low whole grain and low calcium intake (Clinton et al. 2020). The pathogenesis of CRC is depicted in Figure 3.

Microbiome and Colorectal Cancer

Dysbiosis in Colorectal Cancer (CRC)

The composition of microbiota in CRC patients shifts as compared to those in healthy individuals. This shift includes the enrichment of *Bacteroides fragilis* (*B. fragilis*), *Escherichia coli* (*E. Coli*), *Enterococcus faecalis (E. faecalis), Streptococcus gallolyticus* (Wong and Yu 2019), as well as oral bacteria such as *Fusobacterium nucleatum (F. nucleatum), Parvimonas, Peptostreptococcus*, and *Porphyromonas* in fecal and tumor samples from patients with CRC (Feng et al. 2015; Flemer et al. 2017; Kostic et al. 2013; Nakatsu et al. 2015; Thomas et al. 2019; Wirbel et al. 2019; Yachida et al. 2019; Yu et al. 2015; Zeller et al. 2014). However, there are inter-individual differences in the CRC microbiota across geographical locations. Meta-analyses of various studies have identified enrichment of 29 species in CRC microbiota across eight geographical locations (Wirbel et al. 2019). Stage-specific analyses have shown that some bacteria such as *Fusobacterium nucleatum* and *Solobacterium moorei* are enriched progressively from early to late stages of CRC while other species such as *Atopobium parvulum* is enriched in adenoma, that is a precursor to CRC.

Apart from bacteria, viruses from the gut microbiota have also been associated with CRC. For examples, cytomegalovirus, John Cunningham (JC) virus, and human papillomavirus have been positively associated with CRC samples (Cheng et al. 1995; Harkins et al. 2002; Laghi et al. 1999). However, these associations are inconsistent as other studies have not confirmed these findings (Gornick et al. 2010; Hart et al. 1982; Knösel et al. 2004). Nonetheless, an untargeted metagenomic analysis of stool samples found that the gut DNA virome of CRC patients was altered as compared to that of healthy controls (Nakatsu et al. 2018). Of these, 22 viral taxa including cytomegalovirus and bacteriophages could differentiate CRC patients from the healthy controls (Nakatsu et al. 2018).

Another study also found that temperate bacteriophages are associated with CRC (Hannigan et al. 2018). Consistent with these human studies, our longitudinal study on a carcinogen-induced CRC mouse model identified bacteriophage genera that are associated with the CRC growth (Li et al. 2022). We found that Brunovirus and Hpunavirus are positively associated with tumor growth whereas members from Lubbockvirus show a negative correlation with tumor growth (Li et al. 2022). This suggests that bacteriophages may play a role in CRC carcinogenesis. However, further investigation is required to understand the mechanism of carcinogenesis.

Dysbiosis and the CRC Carcinogenesis

An early study has shown that germ-free rats treated with the carcinogen, 1,2-dimethylhydrazine, develop fewer colonic tumors compared to conventional rats treated with the carcinogen (Reddy et al. 1974). A later study showed that mice transplanted with fecal microbiota from patients with CRC developed more intestinal polyps than those transplanted with fecal microbiota from healthy individuals (Wong et al. 2017). These studies suggest that colorectal dysbiosis plays a crucial role in CRC carcinogenesis. Each microbe influences CRC carcinogenesis via the following mechanisms.

Genotoxicity: bacterial species such as *E. Coli* (pks$^+$), enterotoxigenic *B. fragilis* (ETBF) and *E. faecalis* are genotoxic. For example, colibactin produced by *E. Coli* (pks$^+$) induces DNA double-strand breaks, aneuploidy and improper cellular division (Cougnoux et al. 2016; Cuevas-Ramos et al. 2010) and promotes CRC carcinogenesis in an APC$^{min/+}$ CRC mouse model (Tomkovich et al. 2017). In response to the colibactin-producing *E. Coli* infection, colon epithelial cells induce the expression of DNA repair protein RAD51 which in turn induces autophagy for lowering the DNA damaged cells (Lucas et al. 2020), thus limiting the bacterium-promotion of carcinogenesis. Consistent with these *in vitro* and *in vivo* data, *E. Coli* (pks$^+$) induces mutation signatures in human colorectal organoids which were previously identified as the CRC-driver mutations (Pleguezuelos-Manzano et al. 2020). In addition, *B. fragilis* toxin produced by ETBF and reactive oxygen species produced by *E. faecalis* induce DNA damage and genomic instability, leading to CRC carcinogenesis (Goodwin et al. 2011; Huycke et al. 2002; Wang and Huycke 2007).

Inflammation. Chronic inflammation is the risk factor for CRC. This is evidenced by the increased risk of CRC for patients who have inflammatory bowel disease (Beaugerie and Itzkowitz 2015). The inflammation observed in sporadic CRC could be initiated by defects of the epithelial barrier in the adenoma (Grivennikov et al. 2012). Barrier defects allow the dysbiotic bacteria to translocate to the mucosa and lamina propria thus triggering pro-inflammatory responses (Grivennikov et al. 2012). For example, *F. nucleatum* stimulates the TLR4-NFkB signaling pathway and triggers myeloid cell infiltration and inflammation in the tumors, leading to the promotion of colorectal carcinogenesis in APC$^{min/+}$ mouse model (Kostic et al. 2013; Wu et al. 2018; Yang et al. 2017). On the other hand, two proteins expressed by *F. nucleatum* have been shown to promote CRC tumorigenesis via direct interactions. FadA adhesin of *F. nucleatum* binds to E-cadherin of the colorectal mucosa and stimulates b-catenin signaling to increase cell proliferation and inflammatory cytokine response, thereby promoting tumor growth in xenograft CRC models (Rubinstein et al. 2013). The other protein, Fap2 of *F. nucleatum*, interacts with TIGIT, a human NK cell inhibitory receptor, leading to the inhibition of NK cell killing of the CRC tumors (Gur et al. 2015). The second example of proinflammatory bacterium is ETBF. *B. fragilis* toxin produced by ETBF activates the T_H17 inflammatory responses and STAT3 signaling pathways thus potentiating CRC carcinogenesis (Wu et al. 2009). Similarly, *Parvimonas micra* induces T_H17 inflammatory responses, promoting CRC carcinogenesis (Zhao et al. 2022). Yet, the bacterial factor responsible for this effect remains unknown. Another example is *Peptostreptococcus anaerobius* (*P. anaerobius*). It activates TLR2 and/or TLR4 pathways to generate reactive oxidative species. This in turn enhances cholesterol synthesis and cell proliferation, leading to the promotion of tumorigenesis (Tsoi et al. 2017). *P. anaerobius* surface protein, PCWBR2, also interacts with the α2/β1 integrins that are overexpressed in human CRC to activate the PI3K-Akt pathway and NFkB, leading to the infiltration of tumor-associated macrophages and granulocytic tumor-associated neutrophils (Long et al. 2019). These inflammatory responses promote tumorigenesis in the APC$^{min/+}$ mouse model (Long et al. 2019).

Summary

GIT malignancies involve a complex interplay of environmental and genetic risk factors. While the complete pathogenesis of this interaction is not completely understood, it is clear that the rising obesity epidemic and westernization of lifestyle increase the risk of these cancers. Toxins such as alcohol and smoking also exhibit a dose-response relationship in increasing the likelihood of GIT cancers hence lifestyle modifications should be targeted at these risk factors. Screening has improved the rates of early detection thereby conferring a better prognosis for upper CI malignancies. While colonoscopy has reduced the rates of CRC, the rise of early-onset CRC highlights the fact that personalized screening strategies are needed in order to identify at-risk populations earlier. These strategies could include the classification of malignancies beyond anatomical sites or subtypes of histology to molecular classification of malignancies. This enables a more precise understanding of the prognosis and treatment outcome.

Key Take Home Messages

1 Cigarette smoking should be stopped and strategies to support cessation put in place at every opportunity on the patient's pathway.
2 Alcohol consumption should be minimised and ideally 10 units or less per week.
3 Strategies to manage excess body weight should be handled by progressive escalation and if needed referral to a medical/endocrine, surgical, nutrition, psychology MDT.
4 Dysbiosis should be managed proactively by both active prevention (diet and prebiotics) and intervention (next generation probiotic) strategies.

Areas for Further Research

1 Development of diagnostic biomarkers for personalized cancer prevention strategies.
2 Development of predictive biomarkers for optimized interventions.
3 Development of prognostic biomarkers for stratification into endoscopy surveillance.

Trusted Websites for Further Reading

https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/signs-and-symptoms.html
https://opa.org.uk/oesophageal-cancer-2
https://www.cancerresearchuk.org/about-cancer/stomach-cancer

References

Abnet, C.C., Lai, B., Qiao, Y.-L. et al. (2005). Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk. *J Natl Cancer Inst* 97 (4): 301–306.

Alam, M., Srivastava, A., Dutta, A., and Sau, A.K. (2018). Biochemical and biophysical studies of Helicobacter pylori arginine decarboxylase, an enzyme important for acid adaptation in host. *IUBMB Life* 70 (7): 658–669.

Alexandre, L., Long, E., and Beales, I.L. (2014). Pathophysiological mechanisms linking obesity and esophageal adenocarcinoma. *World J Gastrointest Pathophysiol* 5 (4): 534.

Alexandrov, L.B., Nik-Zainal, S., Wedge, D.C. et al. (2013). Signatures of mutational processes in human cancer. *Nature* 500 (7463): 415–421.

Allemani, C., Matsuda, T., Di Carlo, V. et al. (2018). Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 391 (10125): 1023–1075.

Almazar, A.E., Penfield, J.D., Saito, Y.A., and Talley, N.J. (2021). Survival times of patients with Menetrier's disease and risk of gastric cancer. *Clin Gastroenterol Hepatol* 19 (4): 707–712.

Álvarez-Álvarez, L., Vitelli-Storelli, F., Rubín-García, M. et al. (2021). Relationship between the risk of gastric cancer and adherence to the Mediterranean diet according to different estimators. MCC—Spain study. *Cancers* 13 (21): 5281.

Aretz, S., Stienen, D., Uhlhaas, S. et al. (2005). High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. *Hum Mutat* 26 (6): 513–519.

Armaghany, T., Wilson, J.D., Chu, Q., and Mills, G. (2012). Genetic alterations in colorectal cancer. *Gastrointest Cancer Res* 5 (1): 19.

Arnold, M., Soerjomataram, I., Ferlay, J., and Forman, D. (2015). Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 64 (3): 381–387.

Bagnoli, F., Buti, L., Tompkins, L. et al. (2005). Helicobacter pylori CagA induces a transition from polarized to invasive phenotypes in MDCK cells. *Proc Natl Acad Sci U S A* 102 (45): 16339–16344. https://doi.org/10.1073/pnas.0502598102.

Barrow, P., Khan, M., Lalloo, F. et al. (2013). Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. *J Br Surg* 100 (13): 1719–1731.

Beaugerie, L. and Itzkowitz, S.H. (2015). Cancers complicating inflammatory bowel disease. *N Engl J Med* 372 (15): 1441–1452. https://doi.org/10.1056/NEJMra1403718.

Beggs, A., Latchford, A.R., Vasen, H.F. et al. (2010). Peutz–Jeghers syndrome: a systematic review and recommendations for management. *Gut* 59 (7): 975–986.

Björk, J., Åkerbrant, H., Iselius, L. et al. (2001). Periampullary adenomas and adenocarcinomas in familial adenomatous polyposis: cumulative risks and APC gene mutations. *Gastroenterology* 121 (5): 1127–1135.

Blackett, K.L., Siddhi, S.S., Cleary, S. et al. (2013). Oesophageal bacterial biofilm changes in gastro-oesophageal reflux disease, Barrett's and oesophageal carcinoma: association or causality? *Aliment Pharmacol Ther* 37 (11): 1084–1092. https://doi.org/10.1111/apt.12317.

Blair, V.R., McLeod, M., Carneiro, F. et al. (2020). Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 21 (8): e386–e397.

Boccia, S., Sayed-Tabatabaei, F.A., Persiani, R. et al. (2007). Polymorphisms in metabolic genes, their combination and interaction with tobacco smoke and alcohol consumption and risk of gastric cancer: a case-control study in an Italian population. *BMC Cancer* 7 (1): 1–8.

Bordi, C., D'adda, T., Azzoni, C. et al. (1995). Hypergastrinemia and gastric enterochromaffin-like cells. *Am J Surg Pathol* 19: S8–19.

Bosman, F. (1999). The hamartoma–adenoma–carcinoma sequence. In Vol. (188, pp. 1–2): Wiley Online Library.

[Record #43 is using a reference type undefined in this output style.]

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 68 (6): 394–424.

Buchner, A.M. and Lichtenstein, G.R. (2016). Evaluation and detection of dysplasia in IBD: the role of chromoendoscopy and enhanced imaging techniques. *Curr Treatm Opt Gastroenterol* 14 (1): 73–82.

Bülow, S., Christensen, I., Højen, H. et al. (2012). Duodenal surveillance improves the prognosis after duodenal cancer in familial adenomatous polyposis. *Colorectal Dis* 14 (8): 947–952.

Burke, C.A., Beck, G.J., Church, J.M., and van Stolk, R.U. (1999). The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gastrointest Endosc* 49 (3): 358–364.

Buti, L., Ruiz-Puig, C., Sangberg, D. et al. (2020). CagA-ASPP2 complex mediates loss of cell polarity and favors H. pylori colonization of human gastric organoids. *Proc Natl Acad Sci U S A* 117 (5): 2645–2655. https://doi.org/10.1073/pnas.1908787117.

Buti, L., Spooner, E., Van der Veen, A.G. et al. (2011). Helicobacter pylori cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. *Proc Natl Acad Sci U S A* 108 (22): 9238–9243. https://doi.org/10.1073/pnas.1106200108.

Buttar, N.S., Wang, K.K., Leontovich, O. et al. (2002). Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. *Gastroenterology* 122 (4): 1101–1112. https://doi.org/10.1053/gast.2002.32371.

Calle, E.E. and Kaaks, R. (2004). Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 4 (8): 579–591.

Chen, H.-Y., Jin, X.-W., Li, B.-R. et al. (2017b). Cancer risk in patients with Peutz–Jeghers syndrome: a retrospective cohort study of 336 cases. *Tumor Biol* 39 (6): 1010428317705131.

Cheng, J.Y., Sheu, L.F., Meng, C.L. et al. (1995). Detection of human papillomavirus DNA in colorectal carcinomas by polymerase chain reaction. *Gut* 37 (1): 87–90. https://doi.org/10.1136/gut.37.1.87.

Choi, Y.-J., Myung, S.-K., and Lee, J.-H. (2018). Light alcohol drinking and risk of cancer: a meta-analysis of cohort studies. *Cancer Res Treat: Off J Korean Cancer Assoc* 50 (2): 474–487.

Chung, J.M., Sheedlo, M.J., Campbell, A.M. et al. (2019). Structure of the Helicobacter pylori Cag type IV secretion system. *Elife* 8. https://doi.org/10.7554/eLife.47644.

Clinton, S.K., Giovannucci, E.L., and Hursting, S.D. (2020). The world cancer research fund/American institute for cancer research third expert report on diet, nutrition, physical activity, and cancer: impact and future directions. *J Nutr* 150 (4): 663–671.

Coati, I., Fassan, M., Farinati, F. et al. (2015). Autoimmune gastritis: pathologist's viewpoint. *World J Gastroenterol* 21 (42): 12179.

Coker, O.O., Dai, Z., Nie, Y. et al. (2018). Mucosal microbiome dysbiosis in gastric carcinogenesis. *Gut* 67 (6): 1024–1032. https://doi.org/10.1136/gutjnl-2017-314281.

Collaborators, G.C.C. (2022). Global, regional, and national burden of colorectal cancer and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol* 7 (7): 627.

Conteduca, V., Sansonno, D., Russi, S., and Dammacco, F. (2013). Precancerous colorectal lesions. *Int J Oncol* 43 (4): 973–984.

Corley, D.A., Kubo, A., Levin, T.R. et al. (2007). Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology* 133 (1): 34–41.

Correa, P., Haenszel, W., Cuello, C. et al. (1975). A model for gastric cancer epidemiology. *Lancet* 306 (7924): 58–60.

Cougnoux, A., Delmas, J., Gibold, L. et al. (2016). Small-molecule inhibitors prevent the genotoxic and protumoural effects induced by colibactin-producing bacteria. *Gut* 65 (2): 278–285. https://doi.org/10.1136/gutjnl-2014-307241.

Cuevas-Ramos, G., Petit, C.R., Marcq, I. et al. (2010). Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. *Proc Natl Acad Sci U S A* 107 (25): 11537–11542. https://doi.org/10.1073/pnas.1001261107.

de Rezende, L.F.M., de Sá, T.H., Markozannes, G. et al. (2018). Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *Br J Sports Med* 52 (13): 826–833.

Deshpande, N.P., Riordan, S.M., Castano-Rodriguez, N. et al. (2018). Signatures within the esophageal microbiome are associated with host genetics, age, and disease. *Microbiome* 6 (1): 227. https://doi.org/10.1186/s40168-018-0611-4.

Dow, L.E., O'Rourke, K.P., Simon, J. et al. (2015). Apc restoration promotes cellular differentiation and reestablishes crypt homeostasis in colorectal cancer. *Cell* 161 (7): 1539–1552.

East, J.E., Atkin, W.S., Bateman, A.C. et al. (2017). British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. *Gut* 66 (7): 1181–1196.

Elliott, D.R.F., Walker, A.W., O'Donovan, M. et al. (2017). A non-endoscopic device to sample the oesophageal microbiota: a case-control study. *Lancet Gastroenterol Hepatol* 2 (1): 32–42. https://doi.org/10.1016/s2468-1253(16)30086-3.

El-Serag, H.B. and Thrift, A.P. (2021). Obesity and gastroesophageal reflux disease. *Esophagus* 624–632.

Etemadi, A., Safiri, S., Sepanlou, S.G. et al. (2020). The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet Gastroenterol Hepatol* 5 (1): 42–54.

Eusebi, L.H., Telese, A., Marasco, G. et al. (2020). Gastric cancer prevention strategies: a global perspective. *J Gastroenterol Hepatol* 35 (9): 1495–1502.

Fakharian, F., Asgari, B., Nabavi-Rad, A. et al. (2022). The interplay between Helicobacter pylori and the gut microbiota: an emerging driver influencing the immune system homeostasis and gastric carcinogenesis. *Front Cell Infect Microbiol* 12: 953718. https://doi.org/10.3389/fcimb.2022.953718.

Fan, X., Qin, X., Zhang, Y. et al. (2021). Screening for gastric cancer in China: advances, challenges and visions. *Chin J Cancer Res* 33 (2): 168.

Feng, Q., Liang, S., Jia, H. et al. (2015). Gut microbiome development along the colorectal adenoma–carcinoma sequence [Article]. *Nat Commun* 6: 6528. https://doi.org/10.1038/ncomms7528. http://www.nature.com/articles/ncomms7528#supplementary-information.

Ferro, A., Costa, A.R., Morais, S. et al. (2020). Fruits and vegetables intake and gastric cancer risk: a pooled analysis within the Stomach cancer Pooling Project. *Int J Cancer* 147 (11): 3090–3101.

Ferro, A., Morais, S., Pelucchi, C. et al. (2019). Smoking and Helicobacter pylori infection: an individual participant pooled analysis (Stomach Cancer Pooling-StoP Project). *Eur J Cancer Prev* 28 (5): 390–396.

Flemer, B., Lynch, D.B., Brown, J.M. et al. (2017). Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut* 66 (4): 633–643. https://doi.org/10.1136/gutjnl-2015-309595.

Flis, E., Barber, G., Nulty, C. et al. (2021). Identification of TLR2 Signalling Mechanisms Which Contribute to Barrett's and Oesophageal Adenocarcinoma Disease Progression. *Cancers (Basel)* 13 (9). https://doi.org/10.3390/cancers13092065.

Furihata, C., Ohta, H., and Katsuyama, T. (1996). Cause and effect between concentration-dependent tissue damage and temporary cell proliferation in rat stomach mucosa by NaCl, a stomach tumor promoter. *Carcinogenesis* 17 (3): 401–406.

Garber, J.E., Goldstein, A.M., Kantor, A.F. et al. (1991). Follow-up study of twenty-four families with Li-Fraumeni syndrome. *Cancer Res* 51 (22): 6094–6097.

Gastli, N., Allain, M., Lamarque, D. et al. (2021). Diagnosis of Helicobacter pylori infection in a routine testing workflow: effect of bacterial load and virulence factors. *J Clin Med* 10 (13): 2755.

Gauthier, N.C., Monzo, P., Kaddai, V. et al. (2005). Helicobacter pylori VacA cytotoxin: a probe for a clathrin-independent and Cdc42-dependent pinocytic pathway routed to late endosomes. *Mol Biol Cell* 16 (10): 4852–4866. https://doi.org/10.1091/mbc.e05-05-0398.

Gergen, A.K., Jarrett, M.J., Li, A. et al. (2021). Toll-like receptor 4 mediates reflux-induced inflammation in a murine reflux model. *Semin Thorac Cardiovasc Surg*. https://doi.org/10.1053/j.semtcvs.2021.07.033.

Giovannucci, E. and Martinez, M.E. (1996). Tobacco, colorectal cancer, and adenomas: a review of the evidence. *J Natl Cancer Inst* 88 (23): 1717–1730.

Goldenring, J.R. and Mills, J.C. (2022). Cellular plasticity, reprogramming, and regeneration: metaplasia in the stomach and beyond. *Gastroenterology* 162 (2): 415–430. https://doi.org/10.1053/j.gastro.2021.10.036.

Goodwin, A.C., Destefano Shields, C.E., Wu, S. et al. (2011). Polyamine catabolism contributes to enterotoxigenic Bacteroides fragilis-induced colon tumorigenesis. *Proc Natl Acad Sci U S A* 108 (37): 15354–15359. https://doi.org/10.1073/pnas.1010203108.

Gornick, M.C., Castellsague, X., Sanchez, G. et al. (2010). Human papillomavirus is not associated with colorectal cancer in a large international study. *Cancer Causes Control* 21 (5): 737–743. https://doi.org/10.1007/s10552-010-9502-0.

Grivennikov, S.I., Wang, K., Mucida, D. et al. (2012). Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth https://doi.org/10.1038/nature11465. *Nature* 491 (7423): 254–258. http://www.nature.com/nature/journal/v491/n7423/abs/nature11465.html#supplementary-information. (Accessed on 10th March 2023)

Group, I.W. (2012). IARC working group on the evaluation of carcinogenic risks to humans: biological agents. Volume 100 B. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 100 (pt B): 1.

Gur, C., Ibrahim, Y., Isaacson, B. et al. (2015). Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity* 42 (2): 344–355. https://doi.org/10.1016/j.immuni.2015.01.010.

Guttenplan, J. (1990). Mutagenesis by N-nitroso compounds: relationships to DNA adducts, DNA repair, and mutational efficiencies. *Mutat Res – Fundam Mol Mech Mutagen* 233 (1–2): 177–187.

Han, J., Jiang, Y., Liu, X. et al. (2015). Dietary fat intake and risk of gastric cancer: a meta-analysis of observational studies. *PLoS One* 10 (9): e0138580.

Hannigan, G.D., Duhaime, M.B., Ruffin, M.T. et al. (2018). Diagnostic potential and interactive dynamics of the colorectal cancer virome. *MBio* 9 (6). https://doi.org/10.1128/mBio.02248-18.

Hansford, S., Kaurah, P., Li-Chang, H. et al. (2015). Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol* 1 (1): 23–32.

Harkins, L., Volk, A.L., Samanta, M. et al. (2002). Specific localisation of human cytomegalovirus nucleic acids and proteins in human colorectal cancer. *Lancet* 360 (9345): 1557–1563. https://doi.org/10.1016/s0140-6736(02)11524-8.

Hart, H., Neill, W.A., and Norval, M. (1982). Lack of association of cytomegalovirus with adenocarcinoma of the colon. *Gut* 23 (1): 21–30. https://doi.org/10.1136/gut.23.1.21.

He, Z., Zhao, Y., Guo, C. et al. (2010). Prevalence and risk factors for esophageal squamous cell cancer and precursor lesions in Anyang, China: a population-based endoscopic survey. *Br J Cancer* 103 (7): 1085–1088.

Hooi, J.K., Lai, W.Y., Ng, W.K. et al. (2017). Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology* 153 (2): 420–429.

Huang, J., Koulaouzidis, A., Marlicz, W. et al. (2021). Global burden, risk factors, and trends of esophageal cancer: an analysis of cancer registries from 48 countries. *Cancers* 13 (1): 141.

Huhta, H., Helminen, O., Lehenkari, P.P. et al. (2016). Toll-like receptors 1, 2, 4 and 6 in esophageal epithelium, Barrett's esophagus, dysplasia and adenocarcinoma. *Oncotarget* 7 (17): 23658–23667. https://doi.org/10.18632/oncotarget.8151.

Huycke, M.M., Abrams, V., and Moore, D.R. (2002). Enterococcus faecalis produces extracellular superoxide and hydrogen peroxide that damages colonic epithelial cell DNA. *Carcinogenesis* 23 (3): 529–536. https://doi.org/10.1093/carcin/23.3.529.

Hvid-Jensen, F., Pedersen, L., Drewes, A.M. et al. (2011). Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 365 (15): 1375–1383.

Ilson, D.H. and van Hillegersberg, R. (2018). Management of patients with adenocarcinoma or squamous cancer of the esophagus. *Gastroenterology* 154 (2): 437–451.

Itzkowitz, S.H. and Yio, X. (2004). Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 287 (1): G7–G17.

Jankowski, J.A., Harrison, R.F., Perry, I. et al. (2000). Barrett's metaplasia. *Lancet* 356 (9247): 2079–2085.

Jass, J., Smyrk, T., Stewart, S. et al. (1994). Pathology of hereditary non-polyposis colorectal cancer. *Anticancer Res* 14 (4B): 1631–1634.

Kalloo, A.N. and Shanahan, F. (2016). *Yamada's Atlas of Gastroenterology*. Wiley Blackwell.

Kanth, P., Grimmett, J., Champine, M. et al. (2017). Hereditary colorectal polyposis and cancer syndromes: a primer on diagnosis and management. *Off J Am College Gastroenterol* 112 (10): 1509–1525.

Kanth, P. and Inadomi, J.M. (2021). Screening and prevention of colorectal cancer. *Bmj* 374.

Karuman, P., Gozani, O., Odze, R.D. et al. (2001). The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death. *Molecular Cell* 7 (6): 1307–1319.

Kedrin, D. and Gala, M.K. (2015). Genetics of the serrated pathway to colorectal cancer. *Clin Transl Gastroenterol* 6 (4): e84.

Keszei, A.P., Goldbohm, R.A., Schouten, L.J. et al. (2013). Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *Am J Clin Nutr* 97 (1): 135–146.

Keum, N. and Giovannucci, E. (2019). Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol* 16 (12): 713–732.

[Record #98 is using a reference type undefined in this output style.]

Kim, S.R., Kim, K., Lee, S.A. et al. (2019). Effect of red, processed, and white meat consumption on the risk of gastric cancer: an overall and dose–response meta-analysis. *Nutrients* 11 (4): 826.

Kim, Y.J., Kim, E.H., and Hahm, K.B. (2012). Oxidative stress in inflammation-based gastrointestinal tract diseases: challenges and opportunities. *J Gastroenterol Hepatol* 27 (6): 1004–1010.

Kneller, R.W., You, W.-C., Chang, Y.-S. et al. (1992). Cigarette smoking and other risk factors for progression of precancerous stomach lesions. *J Natl Cancer Inst* 84 (16): 1261–1266.

Knorr, J., Ricci, V., Hatakeyama, M., and Backert, S. (2019). Classification of Helicobacter pylori Virulence Factors: is CagA a Toxin or Not? *Trends Microbiol* 27 (9): 731–738. https://doi.org/10.1016/j.tim.2019.04.010.

Knösel, T., Schewe, C., Dietel, M., and Petersen, I. (2004). Cytomegalovirus is not associated with progression and metastasis of colorectal cancer. *Cancer Lett* 211 (2): 243–247. https://doi.org/10.1016/j.canlet.2004.02.011.

Kocarnik, J.M., Compton, K., Dean, F.E. et al. (2022). Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *JAMA Oncol* 8 (3): 420–444.

Kory, W. (2010). Jasperson hereditary and familial colon cancer/Kory W. Jasperson [et al.]. *Gastroenterology* 138 (6): 2044–2058.

Kostic, A.D., Chun, E., Robertson, L. et al. (2013). Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 14 (2): 207–215. https://doi.org/10.1016/j.chom.2013.07.007.

Kwak, J.H. and Paik, J.K. (2020). Vitamin D status and gastric cancer: a cross-sectional study in Koreans. *Nutrients* 12 (7): 2004.

Kwon, S.K., Park, J.C., Kim, K.H. et al. (2022). Human gastric microbiota transplantation recapitulates premalignant lesions in germ-free mice. *Gut* 71 (7): 1266–1276. https://doi.org/10.1136/gutjnl-2021-324489.

Lachenmeier, D.W. (2007). Consequences of IARC re-evaluation of alcoholic beverage consumption and ethyl carbamate on food control. *Dtsch Lebensmitt Rundsch* 103 (7): 307.

Laghi, L., Randolph, A.E., Chauhan, D.P. et al. (1999). JC virus DNA is present in the mucosa of the human colon and in colorectal cancers. *Proc Natl Acad Sci U S A* 96 (13): 7484–7489. https://doi.org/10.1073/pnas.96.13.7484.

Lahner, E., Esposito, G., Galli, G., and Annibale, B. (2015). Atrophic gastritis and pre-malignant gastric lesions. *Transl Gastrointest Cancer* 4 (4): 272–281.

Laszkowska, M., Rodriguez, S., Kim, J., and Hur, C. (2021). Heavy alcohol use is associated with gastric cancer: analysis of the national health and nutrition examination survey from 1999 to 2010. *Off J Am College Gastroenterol* 116 (5): 1083–1086.

Latchford, A., Neale, K., Phillips, R., and Clark, S. (2011). Peutz-Jeghers syndrome: intriguing suggestion of gastrointestinal cancer prevention from surveillance. *Dis Colon Rectum* 54 (12): 1547–1551.

Lee, C.W., Rickman, B., Rogers, A.B. et al. (2008). Helicobacter pylori eradication prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. *Cancer Res* 68 (9): 3540–3548. https://doi.org/10.1158/0008-5472.Can-07-6786.

Lertpiriyapong, K., Whary, M.T., Muthupalani, S. et al. (2014). Gastric colonisation with a restricted commensal microbiota replicates the promotion of neoplastic lesions by diverse intestinal microbiota in the Helicobacter pylori INS-GAS mouse model of gastric carcinogenesis. *Gut* 63 (1): 54–63. https://doi.org/10.1136/gutjnl-2013-305178.

Li, J., Xu, J., Zheng, Y. et al. (2021). Esophageal cancer: epidemiology, risk factors and screening. *Chin J Cancer Res* 33 (5): 535.

Li, Y., Zhang, F., Zheng, H. et al. (2022). Fecal DNA virome is associated with the development of colorectal neoplasia in a murine model of colorectal cancer. *Pathogens* 11 (4). https://doi.org/10.3390/pathogens11040457.

Lin, D.-C., Hao, -J.-J., Nagata, Y. et al. (2014a). Genomic and molecular characterization of esophageal squamous cell carcinoma. *Nat Genet* 46 (5): 467–473.

Liu, C., Ng, S.K., Ding, Y. et al. (2022). Meta-analysis of mucosal microbiota reveals universal microbial signatures and dysbiosis in gastric carcinogenesis. *Oncogene* 41 (28): 3599–3610. https://doi.org/10.1038/s41388-022-02377-9.

Lofgren, J.L., Whary, M.T., Ge, Z. et al. (2011). Lack of commensal flora in Helicobacter pylori-infected INS-GAS mice reduces gastritis and delays intraepithelial neoplasia. *Gastroenterology* 140 (1): 210–220. https://doi.org/10.1053/j.gastro.2010.09.048.

Long, X., Wong, C.C., Tong, L. et al. (2019). Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. *Nat Microbiol* 4 (12): 2319–2330. https://doi.org/10.1038/s41564-019-0541-3.

Lopetuso, L.R., Severgnini, M., Pecere, S. et al. (2020). Esophageal microbiome signature in patients with Barrett's esophagus and esophageal adenocarcinoma. *PLoS One* 15 (5): e0231789. https://doi.org/10.1371/journal.pone.0231789.

Lucas, C., Salesse, L., Hoang, M.H.T. et al. (2020). Autophagy of intestinal epithelial cells inhibits colorectal carcinogenesis induced by colibactin-producing escherichia coli in Apc(Min/+) mice. *Gastroenterology* 158 (5): 1373–1388. https://doi.org/10.1053/j.gastro.2019.12.026.

Luo, G., Zhang, Y., Guo, P. et al. (2017). Global patterns and trends in stomach cancer incidence: age, period and birth cohort analysis. *Int J Cancer* 141 (7): 1333–1344.

Lynch, H.T. and De la Chapelle, A. (2003). Hereditary colorectal cancer. *N Engl J Med* 348 (10): 919–932.

Markowitz, S.D. and Bertagnolli, M.M. (2009). Molecular basis of colorectal cancer. *N Engl J Med* 361 (25): 2449–2460.

Masciari, S., Dewanwala, A., Stoffel, E.M. et al. (2011). Gastric cancer in individuals with Li-Fraumeni syndrome. *Genet Med* 13 (7): 651–657.

Mathieu, L.N., Kanarek, N.F., Tsai, H.-L. et al. (2014). Age and sex differences in the incidence of esophageal adenocarcinoma: results from the Surveillance, Epidemiology, and End Results (SEER) Registry (1973–2008). *Diseases Esophagus* 27 (8): 757–763.

Matsumoto, A., Isomoto, H., Nakayama, M. et al. (2011). Helicobacter pylori VacA reduces the cellular expression of STAT3 and pro-survival Bcl-2 family proteins, Bcl-2 and Bcl-XL, leading to apoptosis in gastric epithelial cells. *Dig Dis Sci* 56 (4): 999–1006. https://doi.org/10.1007/s10620-010-1420-1.

Migliore, L., Migheli, F., Spisni, R., and Coppedè, F. (2011). Genetics, cytogenetics, and epigenetics of colorectal cancer. *J Biomed Biotechnol* 2011.

Monahan, K.J., Bradshaw, N., Dolwani, S. et al. (2020). Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer genetics group (UKCGG). *Gut* 69 (3): 411–444.

Morais, S., Costa, A., Albuquerque, G. et al. (2022). Salt intake and gastric cancer: a pooled analysis within the Stomach cancer Pooling (StoP) Project. *Cancer Causes Control* 33 (5): 779–791.

Morgan, E., Arnold, M., Camargo, M.C. et al. (2022a). The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: a population-based modelling study. *EClinicalMedicine* 47: 101404.

Morgan, E., Soerjomataram, I., Rumgay, H. et al. (2022b). The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. *Gastroenterology* 163 (3): 649–658. e642.

Nakatsu, G., Li, X., Zhou, H. et al. (2015). Gut mucosal microbiome across stages of colorectal carcinogenesis [Article]. *Nat Commun* 6: 8727. https://doi.org/10.1038/ncomms9727. http://www.nature.com/articles/ncomms9727#supplementary-information.

Nakatsu, G., Zhou, H., Wu, W.K.K. et al. (2018). Alterations in enteric virome associate with colorectal cancer and survival outcomes. *Gastroenterology*. https://doi.org/10.1053/j.gastro.2018.04.018.

Nashimoto, A., Akazawa, K., Isobe, Y. et al. (2013). Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer* 16 (1): 1–27.

Nucci, D., Marino, A., Realdon, S. et al. (2021). Lifestyle, WCRF/AICR recommendations, and esophageal adenocarcinoma risk: a systematic review of the literature. *Nutrients* 13 (10): 3525.

Ogunwobi, O., Mutungi, G., and Beales, I.L. (2006). Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cyclooxygenase-2-dependent, prostaglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. *Endocrinology* 147 (9): 4505–4516.

Ouchi, N., Parker, J.L., Lugus, J.J., and Walsh, K. (2011). Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 11 (2): 85–97.

Pandeya, N., Olsen, C.M., and Whiteman, D.C. (2013). Sex differences in the proportion of esophageal squamous cell carcinoma cases attributable to tobacco smoking and alcohol consumption. *Cancer Epidemiol* 37 (5): 579–584.

Pandeya, N., Williams, G., Green, A.C. et al. (2009). Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. *Gastroenterology* 136 (4): 1215–1224. e1212.

Patel, S.G. and Ahnen, D.J. (2012). Familial colon cancer syndromes: an update of a rapidly evolving field. *Curr Gastroenterol Rep* 14 (5): 428–438.

Pearlman, R., Frankel, W.L., Swanson, B. et al. (2017). Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol* 3 (4): 464–471.

Pei, Z., Bini, E.J., Yang, L. et al. (2004). Bacterial biota in the human distal esophagus. *Proc Natl Acad Sci U S A* 101 (12): 4250–4255. https://doi.org/10.1073/pnas.0306398101.

Petrick, J.L., Falk, R.T., Hyland, P.L. et al. (2018). Association between circulating levels of sex steroid hormones and esophageal adenocarcinoma in the FINBAR Study. *PLoS One* 13 (1): e0190325.

Plawski, A., Banasiewicz, T., Borun, P. et al. (2013). Familial adenomatous polyposis of the colon. *Hered Cancer Clin Pract* 11 (1): 1–9.

Pleguezuelos-Manzano, C., Puschhof, J., Huber, A.R. et al., (2020). Mutational signature in colorectal cancer caused by genotoxic pks(+) E. coli. *Nature*. https://doi.org/10.1038/s41586-020-2080-8 (Accessed on 10th March 2023).

Plummer, M., Franceschi, S., Vignat, J. et al. (2015). Global burden of gastric cancer attributable to Helicobacter pylori. *Int J Cancer* 136 (2): 487–490.

Pocurull, A., Herrera-Pariente, C., Carballal, S. et al. (2021). Clinical, molecular and genetic characteristics of early onset gastric cancer: analysis of a large multicenter study. *Cancers* 13 (13): 3132.

Pohl, H., Sirovich, B., and Welch, H.G. (2010). Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 19 (6): 1468–1470.

Praud, D., Rota, M., Pelucchi, C. et al. (2018). Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project. *Eur J Cancer Prev* 27 (2): 124–133.

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Rajendra, S., Wang, B., Snow, E.T. et al. (2013). Transcriptionally active human papillomavirus is strongly associated with Barrett's dysplasia and esophageal adenocarcinoma. *Am J Gastroenterol* 108 (7): 1082–1093. https://doi.org/10.1038/ajg.2013.94.

Rawla, P. and Barsouk, A. (2019). Epidemiology of gastric cancer: global trends, risk factors and prevention. *Gastroenterol Rev Przeglad Gastroenterologiczny* 14 (1): 26–38.

Reddy, B.S., Weisburger, J.H., Narisawa, T., and Wynder, E.L. (1974). Colon carcinogenesis in germ-free rats with 1,2-dimethylhydrazine and N-methyl-n'-nitro-N-nitrosoguanidine. *Cancer Res* 34 (9): 2368–2372.

Roberts, D.L., Dive, C., and Renehan, A.G. (2010). Biological mechanisms linking obesity and cancer risk: new perspectives. *Ann Rev Med* 61: 301–316.

Rock, C.L., Thomson, C., Gansler, T. et al. (2020). American cancer society guideline for diet and physical activity for cancer prevention. *CA: Cancer J Clin* 70 (4): 245–271.

Rubenstein, J.H. and Taylor, J. (2010). Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Ther* 32 (10): 1222–1227.

Rubinstein, M.R., Wang, X., Liu, W. et al. (2013). Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling via its FadA adhesin. *Cell Host Microbe* 14 (2): 195–206. https://doi.org/10.1016/j.chom.2013.07.012.

Salaspuro, M. (1997). Microbial metabolism of ethanol and acetaldehyde and clinical consequences. *Addict Biol* 2 (1): 35–46.

Seitz, H.K. and Stickel, F. (2007). Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer* 7 (8): 599–612.

Sekiguchi, M., Oda, I., Matsuda, T., and Saito, Y. (2022). Epidemiological trends and future perspectives of gastric cancer in eastern Asia. *Digestion* 103 (1): 22–28.

Sharma, T., Gupta, A., Chauhan, R. et al. (2022). Cross-talk between the microbiome and chronic inflammation in esophageal cancer: potential driver of oncogenesis. *Cancer Metastasis Rev* 41 (2): 281–299. https://doi.org/10.1007/s10555-022-10026-6.

Sheikh, M., Poustchi, H., Pourshams, A. et al. (2019). Individual and combined effects of environmental risk factors for esophageal cancer based on results from the Golestan Cohort Study. *Gastroenterology* 156 (5): 1416–1427.

Shimizu, T., Chiba, T., and Marusawa, H. (2017). Helicobacter pylori-mediated genetic instability and gastric carcinogenesis. *Curr Top Microbiol Immunol* 400: 305–323. https://doi.org/10.1007/978-3-319-50520-6_13.

Siegel, R.L., Miller, K.D., and Jemal, A. (2019). Cancer statistics, 2019. *CA: Cancer J Clin* 69 (1): 7–34.

Silva, A.C., Vicentini, M.F.B., Mendoza, E.Z. et al. (2019). Young-age onset colorectal cancer in Brazil: analysis of incidence, clinical features, and outcomes in a tertiary cancer center. *Curr Probl Cancer* 43 (5): 477–486.

Singh, S., Sharma, A.N., Murad, M.H. et al. (2013). Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 11 (11): 1399–1412.

Sjomina, O., Pavlova, J., Niv, Y., and Leja, M. (2018). Epidemiology of helicobacter pylori infection. *Helicobacter* 23: e12514.

Snider, E.J., Compres, G., Freedberg, D.E. et al. (2019). Alterations to the esophageal microbiome associated with progression from Barrett's esophagus to esophageal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 28 (10): 1687–1693. https://doi.org/10.1158/1055-9965.Epi-19-0008.

Song, M., Hu, F.B., Spiegelman, D. et al. (2016). Long-term status and change of body fat distribution, and risk of colorectal cancer: a prospective cohort study. *Int J Epidemiol* 45 (3): 871–883.

Song, X., Xin, N., Wang, W., and Zhao, C. (2015b). Wnt/β-catenin, an oncogenic pathway targeted by H. pylori in gastric carcinogenesis. *Oncotarget* 6 (34): 35579.

Song, Y., Li, L., Ou, Y. et al. (2014). Identification of genomic alterations in oesophageal squamous cell cancer. *Nature* 509 (7498): 91–95.

Sonnenberg, A. (2013). Historic changes of helicobacter pylori-associated diseases. *Aliment Pharmacol Ther* 38 (4): 329–342.

Steevens, J., Schouten, L.J., Driessen, A.L. et al. (2010). Toenail selenium status and the risk of Barrett's esophagus: the Netherlands cohort study. *Cancer Causes Control* 21 (12): 2259–2268.

Stefanski, C.D. and Prosperi, J.R. (2020). Wnt-independent and Wnt-dependent effects of APC loss on the chemotherapeutic response. *Int J Mol Sci* 21 (21): 7844.

Stewart, O.A., Wu, F., and Chen, Y. (2020). The role of gastric microbiota in gastric cancer. *Gut Microbes* 11 (5): 1220–1230. https://doi.org/10.1080/19490976.2020.1762520.

Stoffel, E.M. and Murphy, C.C. (2020). Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. *Gastroenterology* 158 (2): 341–353.

Sukocheva, O.A., Li, B., Due, S.L. et al. (2015). Androgens and esophageal cancer: what do we know? *World J Gastroenterol* 21 (20): 6146.

Sung, H., Ferlay, J., Siegel, R.L. et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 71 (3): 209–249.

Supajatura, V., Ushio, H., Wada, A. et al. (2002). Cutting edge: vacA, a vacuolating cytotoxin of Helicobacter pylori, directly activates mast cells for migration and production of proinflammatory cytokines. *J Immunol* 168 (6): 2603–2607. https://doi.org/10.4049/jimmunol.168.6.2603.

Tayler, R. and Piper, D. (1977). The carcinogenic effect of cigarette smoke: the effect of cigarette smoke on human gastric mucosal cells in organ culture. *Cancer* 39 (6): 2520–2523.

Then, E.O., Lopez, M., Saleem, S. et al. (2020). Esophageal cancer: an updated surveillance epidemiology and end results database analysis. *World J Oncol* 11 (2): 55.

Thomas, A.M., Manghi, P., Asnicar, F. et al. (2019). Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nat Med* 25 (4): 667–678. https://doi.org/10.1038/s41591-019-0405-7.

Thrift, A.P. (2021). Global burden and epidemiology of Barrett oesophagus and oesophageal cancer. *Nat Rev Gastroenterol Hepatol* 18 (6): 432–443.

Thrift, A.P. and Nguyen, T.H. (2021). Gastric cancer epidemiology. *Gastrointest Endosc Clin* 31 (3): 425–439.

Toh, J.W. and Wilson, R.B. (2020). Pathways of gastric carcinogenesis, Helicobacter pylori virulence and interactions with antioxidant systems, vitamin C and phytochemicals. *Int J Mol Sci* 21 (17): 6451.

Toller, I.M., Neelsen, K.J., Steger, M. et al. (2011). Carcinogenic bacterial pathogen Helicobacter pylori triggers DNA double-strand breaks and a DNA damage response in its host cells. *Proc Natl Acad Sci U S A* 108 (36): 14944–14949. https://doi.org/10.1073/pnas.1100959108.

Tomkovich, S., Yang, Y., Winglee, K. et al. (2017). Locoregional effects of microbiota in a preclinical model of colon carcinogenesis. *Cancer Res* 77 (10): 2620–2632. https://doi.org/10.1158/0008-5472.can-16-3472.

Toubia, N. and Schubert, M.L. (2008). Menetrier's disease. *Curr Treatm Opt Gastroenterol* 11 (2): 103–108.

Tsoi, H., Chu, E.S.H., Zhang, X. et al. (2017). Peptostreptococcus anaerobius induces intracellular cholesterol biosynthesis in colon cells to induce proliferation and causes dysplasia in mice. *Gastroenterology* 152 (6): 1419–1433.e1415. https://doi.org/10.1053/j.gastro.2017.01.009.

Uhlenhopp, D.J., Then, E.O., Sunkara, T., and Gaduputi, V. (2020). Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. *J Clin Gastroenterol* 13 (6): 1010–1021.

van Leerdam, M.E., Roos, V.H., van Hooft, J.E. et al. (2019). Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 51 (09): 877–895.

Vaughan, T.L. and Fitzgerald, R.C. (2015). Precision prevention of oesophageal adenocarcinoma. *Nat Rev Gastroenterol Hepatol* 12 (4): 243–248.

Verbeek, R.E., Siersema, P.D., Ten Kate, F.J. et al. (2014). Toll-like receptor 4 activation in Barrett's esophagus results in a strong increase in COX-2 expression. *J Gastroenterol* 49 (7): 1121–1134. https://doi.org/10.1007/s00535-013-0862-6.

Verbeek, R.E., Siersema, P.D., Vleggaar, F.P. et al. (2016). Toll-like receptor 2 signaling and the lysosomal machinery in Barrett's esophagus. *J Gastrointestin Liver Dis* 25 (3): 273–282. https://doi.org/10.15403/jgld.2014.1121.253.rc2.

Vuik, F.E., Nieuwenburg, S.A., Bardou, M. et al. (2019). Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 68 (10): 1820–1826.

Waldum, H.L. and Fossmark, R. (2019). Role of autoimmune gastritis in gastric cancer. *Clin Transl Gastroenterol* 10 (9).

Wang, X. and Huycke, M.M. (2007). Extracellular superoxide production by Enterococcus faecalis promotes chromosomal instability in mammalian cells. *Gastroenterology* 132 (2): 551–561. https://doi.org/10.1053/j.gastro.2006.11.040.

Weise, F., Vieth, M., Reinhold, D. et al. (2020). Gastric cancer in autoimmune gastritis: a case-control study from the German centers of the staR project on gastric cancer research. *United Eur Gastroenterol J* 8 (2): 175–184.

Wen, X., Wen, D., Yang, Y. et al. (2017). Urban-rural disparity in helicobacter pylori infection–related upper gastrointestinal cancer in china and the decreasing trend in parallel with socioeconomic development and urbanization in an endemic area. *Ann Glob Health* 83 (3–4): 444–462.

Willhite, D.C. and Blanke, S.R. (2004). Helicobacter pylori vacuolating cytotoxin enters cells, localizes to the mitochondria, and induces mitochondrial membrane permeability changes correlated to toxin channel activity. *Cell Microbiol* 6 (2): 143–154. https://doi.org/10.1046/j.1462-5822.2003.00347.x.

Win, A.K., Jenkins, M.A., Dowty, J.G. et al. (2017). Prevalence and penetrance of major genes and polygenes for colorectal cancer prevalence and penetrance of major genes and polygenes for CRC. *Cancer Epidemiol Biomarkers Prev* 26 (3): 404–412.

Winawer, S.J., Fletcher, R.H., Miller, L. et al. (1997). Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 112 (2): 594–642.

Wirbel, J., Pyl, P.T., Kartal, E. et al. (2019). Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nat Med*. https://doi.org/10.1038/s41591-019-0406-6.

Wong, S.H. and Yu, J. (2019). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol* 16 (11): 690–704. https://doi.org/10.1038/s41575-019-0209-8.

Wong, S.H., Zhao, L., Zhang, X. et al. (2017). Gavage of fecal samples from patients with colorectal cancer promotes intestinal carcinogenesis in germ-free and conventional mice. *Gastroenterology*. https://doi.org/10.1053/j.gastro.2017.08.022.

Wu, S., Rhee, K.J., Albesiano, E. et al. (2009). A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med* 15 (9): 1016–1022. https://doi.org/10.1038/nm.2015.

Wu, Y., Song, Z., Deng, G. et al. (2021). Gastric acid powered nanomotors release antibiotics for in vivo treatment of Helicobacter pylori infection. *Small* 17 (11): 2006877.

Wu, Y., Wu, J., Chen, T. et al. (2018). Fusobacterium nucleatum Potentiates Intestinal Tumorigenesis in Mice via a Toll-Like Receptor 4/p21-Activated Kinase 1 Cascade. *Dig Dis Sci* 63 (5): 1210–1218. https://doi.org/10.1007/s10620-018-4999-2.

Xi, Y. and Xu, P. (2021). Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol* 14 (10): 101174.

Yachida, S., Mizutani, S., Shiroma, H. et al. (2019). Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. *Nat Med*. https://doi.org/10.1038/s41591-019-0458-7.

Yang, F., Xu, Y., Liu, C. et al. (2018). NF-κB/miR-223-3p/ARID1A axis is involved in Helicobacter pylori CagA-induced gastric carcinogenesis and progression. *Cell Death Dis* 9 (1): 12. https://doi.org/10.1038/s41419-017-0020-9.

Yang, J., Gurudu, S.R., Koptiuch, C. et al. (2020). American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. *Gastrointest Endosc* 91 (5): 963–982. e962.

Yang, X., Zhong, J., Zhang, Q. et al. (2021b). Advances and insights of APC-Asef inhibitors for metastatic colorectal cancer therapy. *Front Mol Biosci* 8: 662579.

Yang, Y., Weng, W., Peng, J. et al. (2017). Fusobacterium nucleatum increases proliferation of colorectal cancer cells and tumor development in mice by activating toll-like receptor 4 signaling to nuclear factor-kappaB, and up-regulating expression of MicroRNA-21. *Gastroenterology* 152 (4): 851–866.e824. https://doi.org/10.1053/j.gastro.2016.11.018.

Yu, J., Feng, Q., Wong, S.H. et al. (2015). Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*. https://doi.org/10.1136/gutjnl-2015-309800.

Zeller, G., Tap, J., Voigt, A.Y. et al. (2014). Potential of fecal microbiota for early-stage detection of colorectal cancer. *Mol Syst Biol* 10 (11). https://doi.org/10.15252/msb.20145645.

Zhang, D., Dai, C., Zhou, L. et al. (2020). Meta-analysis of the association between nut consumption and the risks of cancer incidence and cancer-specific mortality. *Aging (Albany NY)* 12 (11): 10772.

Zhang, W., Zhu, H., Liu, X. et al. (2014). Epidermal growth factor receptor is a prognosis predictor in patients with esophageal squamous cell carcinoma. *Ann Thorac Surg* 98 (2): 513–519.

Zhang, Y., Weck, M.N., Schöttker, B. et al. (2013). Gastric Parietal Cell Antibodies, Helicobacter Pylori Infection, and Chronic Atrophic Gastritis: evidence from a Large Population-based Study in GermanyHelicobacter Pylori Infection, Gastric Parietal Cell Antibodies, and Chronic Atrophic Gastritis. *Cancer Epidemiol Biomarkers Prev* 22 (5): 821–826.

Zhao, L., Zhang, X., Zhou, Y. et al. (2022). Parvimonas micra promotes colorectal tumorigenesis and is associated with prognosis of colorectal cancer patients. *Oncogene* 41 (36): 4200–4210. https://doi.org/10.1038/s41388-022-02395-7.

Zheng, R., Sun, K., Zhang, S. et al. (2019). Report of cancer epidemiology in China, 2015. *Zhonghua zhong liu za zhi [Chin J Oncol]* 41 (1): 19–28.

Zhou, J., Shrestha, P., Qiu, Z. et al. (2020). Distinct microbiota dysbiosis in patients with non-erosive reflux disease and esophageal adenocarcinoma. *J Clin Med* 9 (7). https://doi.org/10.3390/jcm9072162.

Zhou, Z., Bandla, S., Ye, J. et al. (2014). Cyclin E involved in early stage carcinogenesis of esophageal adenocarcinoma by SNP DNA microarray and immunohistochemical studies. *BMC Gastroenterol* 14 (1): 1–8.

2 Genomics, Molecular Pathology, and Pathology of Esophageal and Gastric Cancer

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[Aspects of environmental risk factors are covered in Chapter 1].
[Aspects of relevant colorectal data are covered in Chapter 10].

A) Molecular Pathology of Gastroesophageal Cancers (GECs)

1. Molecular Therapeutic Targets

Over one million of GECs (gastroesophageal cancers) are diagnosed each year worldwide. Comparing all cancer types about 3% are located in the esophagus and about 6% in the stomach. Furthermore, the mortality rate is also unacceptable with a worldwide mortality rate of approximately 80% of patients with GEC die within five years after diagnosis. In 2020, of all cancer deaths 13.2% were GEC caused, whereas regardless of cancer subtype the survival-rate of patients is still very low everywhere (Global Cancer observatory 2020). Therefore, effective treatments for these malignancies still have to be elucidated. The most common type of GEC is adenocarcinoma, which demonstrates extreme heterogeneity due to morphological, molecular and gene expression differences.

The first detailed pathological description of the metaplasia-dysplasia-adenocarcinoma sequence allowed a clear sequential molecular pathological chain of progression to be delineated (Jankowski et al. 1999). Since the first Genome Wise Analysis of Barrett's Esophagus and its associated Esophageal Adenocarinoma were first characterized (Jankowski and Satsangi 2013; Su et al. 2012), rapid progress has been made of the diagnostic, prognostic, and even predictive genetic biomarkers.

In GEC cell signaling several growth factor receptors have been found to play an important role as potential molecular therapeutic targets (overview in Figure 1).

a) **HER-2:** The human epidermal growth factor receptor 2 (HER-2) overexpression is detectable in approximately 30% of all GE (gastroesophageal) adenocarcinomas. Although HER-2 is not an independent prognostic factor, HER-2-positive unresectable or metastatic/recurrent tumors seem to have a favorable prognosis, compared to a HER-2 negative tumor (Janjigian et al. 2012). HER-2 status upfront testing is recommended by expert guidelines, as well as a subsequent combination therapy in HER-2 positive gastric malignancies (Bartley et al. 2016). HER-2 (also called ERBB2) overexpression is tested primary via immunohistochemistry using antibodies, but if the result is equivocal an in situ hybridization for HER-2 is recommended.

The humanized monoclonal anti-HER-2 antibody Trastuzumab (Herceptin, Genentech) was approved for first line therapy for HER-2 positive advanced gastric or gastro-esophageal junction cancer. Several studies of Trastuzumab either with various combinations with chemotherapies or rising dosing were performed in a neoadjuvant setting. However, neither the second line therapy with Trastuzumab, nor an increased dosage were successful. Another monoclonal antibody for HER-2 is Pertizumab (Perjeta, Genentech). A synergetic effect for Trastuzumab was observed not only in combination with Pertizumab, but also with other HER-2 antibodies (e.g., H2-18), which can even overcome GE resistance mechanisms for Trastuzumab (Wang et al. 2021). In contrary to extracellular action of antibodies, also intracellular attempts were made to interrupt the HER-2 signaling pathway, via Tyrosine Kinase Inhibitors (TKIs). One representative, which had been studied, is Lapatinib. However, this resulted in no improvement of the combined chemotherapy.

b) **EGFR:** The Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein with an intracellular tyrosine kinase domain. It is activated in a variety of malignancies and leads to cell proliferation, angiogenesis and

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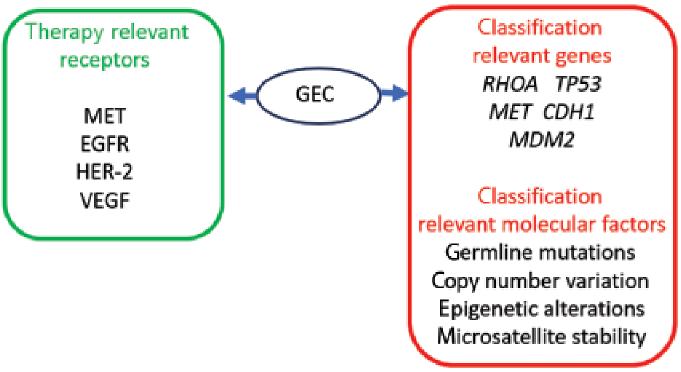


Figure 1 Overview of the therapy relevant growth factor receptors (green box) and molecular classification criteria for intestinal GEC (iGEC) and diffuse GEC (dGEC) (red box) in the gastroesophageal cancer (GEC).

apoptosis resistance. In 40–80% of esophageal cancers an EGFR overexpression was observed (Tew et al. 2005). The EGFR pathway can be interrupted by either EGFR antibodies (e.g., Cetuximab) or TKIs, which led in several malignancies to good therapeutic results. In contrast to that in GEC, targeting the EGFR was rather disappointing with low improvement in overall survival (OS) or progression free survival (PFS) for studies including EGFR antibody or TKIs (Ilson et al. 2014). Therefore, up to now the EGFR targeted therapy is of no use for GE cancer treatment.

c) **VEGF**: The Vascular Endothelial Growth Factor can promote the growth of blood vessels via influencing gene expression and therefore regulates angiogenesis and vascular permeability in the cancer (Shibuya 2011). It preferentially utilizes the PLCγ-PKC-MAPK pathway for signaling and is therefore an interesting target for an anti-angiogenic therapy. Several studies could show in aggressive GECs a VEGF overexpression. Therefore, the high VEGF-expression level is linked with a poor prognosis in GECs (Wei et al. 2017). Moreover, it is proposed to use VEGF-A as a biomarker in this content.

Additionally, several inhibitors for the VEGF were analyzed in different studies, which included antibodies for the VEGF receptor as competitors for the VEGF molecule (e.g., Ramucirumab), as well as TKIs (e.g., Bevacizuma) (Shen et al. 2015). Whereas the TKIs showed ambiguous results which seem to offer little benefit all in all, the antibody approach was more successful. Ramucirumab is a monoclonal antibody, which was tested in several studies with esophageal and gastric cancer. As a second line therapy after progression on chemotherapy the antibody was approved to be used as a single agent (Yoon et al. 2016; Wilke et al. 2014).

d) **MET**: The MET or hepatocyte growth factor receptor (HGFR) is a transmembrane protein with an intracellular tyrosine kinase domain. The receptor part is activated by the Hepatocyte growth factor (HGF) und causes via downstream signaling the activation of several oncogenes that are responsible for angiogenesis, proliferation, and invasion (Cecchi et al. 2012) Among the overexpressed proteins HER-2, EGFR and MET, the latter showed the highest correlation with poor prognosis (Lennerz et al. 2011). Various MET receptor inhibitors were analyzed in studies and with receptor binding molecules, but led to little success.

e) **Immunotherapy:** The gene expression signature in immune cells and the tumor microenvironment (TME) showed a local immune resistance in the area of GECs. The immune resistance is a complex escape mechanism in the cancer cells which leads to a lack of cancer recognition by the immune system. An important mechanism, as a part of the immune resistance, is the angiogenesis and immunosuppressive responses within the tumor tissue. This immunosuppressive microenvironment is created by several cellular mechanisms and soluble factors, such as growth factor receptors (e.g., vascular endothelial growth factor A VEGFA). Therefore, the immunotherapies would benefit from combination therapies with several immune checkpoint agents to reverse the immunosuppressive microenvironment status (Refolo et al. 2020). Immune checkpoint inhibitors as Ipilimumab (Bristol-Meyer Squibb), Nivolimab (Bristol-Meyer Squibb), and Pembrolzumab (Merck), which bind to the anti-programmed death 1 (PD-1) receptor (binding also its ligand PD-L1) have been studied independently and in combination. These studies revealed that the combination of increased PD-L1 expression and microsatellite instability (caused by mismatch repair deficiency) correlate with an increased response to the Nivolimab and Ipilimumab combination therapy (Le et al. 2015; Muro et al. 2015).

2. The Molecular Classification of the GEC

Infection-based sporadic GECs with a previous atopic gastritis are caused by *Helicobacter pylori*, or induced by a reactivation of the latent persisting Epstein-Barr virus (EBV). In fact, *Helicobacter pylori* (HP) provides here the greatest risk factor for GEC and therefore has been extensively studied. The HP infection causes global methylations of CpG islands in the promotor-related regions of the cancer tissue and thus induces cancer. For instance, the methylation of the MLH-1 promotor leads to a loss of gene expression of the MLH-1 genes. The MLH-1 genes code for the mismatch repair protein MLH-1 and dimerizes with PMS2 to a heterodimer. A loss of this heterodimer and therefore a mismatch repair defect in the process of the DNA replication during cell division is one possible reason for microsatellite instability (MSI). MSI in GEC and other cancer types, like the colon carcinoma and a minority of esophageal cancers is associated with the Lynch syndrome. This is an inherited condition that increases the risk of carcinoma in the gastric and colorectal areas and therefore can only be diagnosed by a human geneticist. Thus it is extraordinary important to make Lynch syndrome diagnosis as early as possible.

Several molecular classifications have been proposed in recent years. One gene expression study of 29 genes involved in the immune response mechanism, proposed a GEC classification in the subtypes PD-L1 positive, EBV positive and microsatellite instable (MSI) as well as the amount of tumor infiltrating lymphocytes as a prognostic factor (Park et al. 2017). In contrary the classification of the Asian Cancer Research Group (ACRG) includes four subtypes, based on the gene expression profiles of MSI, MSS/EMT (microsatellite stable/epithelial-to-mesenchymal transition), MSS/TP53+ (TP53 active) and MSS/TP53- (TP53 inactive) (see Figure 2) (Rodriquenz et al. 2020).

However, The Cancer Genome Atlas (TCGA) contains a more comprehensive overview for the genetic pathways of GEC. Here in Figure 3 the following categorization in four subtypes is presented: Epstein-Barr virus positive (EBV), microsatellite instable (MSI), genomically stable (GS) and chromosomal instability (CIN) (Cancer Genome Atlas Research Network 2014).

A common ground for both ACRG and TCGA is the separate subtype for MSI GEC. In GEC the microsatellite instable cancer is associated with a better prognosis and with an increased benefit to immune-based therapies. Except from immune checkpoint inhibitors also other therapeutic approaches such as adoptive T cell transfer, oncocytic viruses, and peptide vaccines are under investigation for MSI GECs (Ratti et al. 2018). Among the other subgroups it is difficult to find a lot of correspondence in the Figures 2 and 3. While the ACRG subtyping pays more attention to the mutations in the TP53 gene and the epithelial-to-mesenchymal transition, the TCGA subtyping is based on more molecular features as chromosomal stability and molecular alterations. These differences may be probably due to the geographic differences in the two population groups (Eastern versus Western patients) and different analysis methods (Rodriquenz et al. 2020).

According to the TCGA classification the two molecular subtypes here, the MSI GEC with promotor methylation and the EBV positive GEC had a higher rate of 10–15% and 30–50% respectively of PD-L1 overexpression. This makes these two subtypes EBV positive and MSI GECs good candidates for immunotherapy (Carneiro et al. 2019). The prognosis of these two subtypes MSI and EBV positive is also better, than of their counterparts (MSS and EBV negative). A histologic feature of the EBV positive GEC is the presence of lymphoid stoma, whereas the genomically stable (GS) subtype corresponds (according to the Laurén histological classification) to the diffuse GEC type and the chromosomal instability (CIN) subtype to the intestinal GEC type. Thus histological characteristics, EBV detection, and MLH-1 promotor methylation analysis are biomarkers of good prognosis (Carneiro et al. 2019).

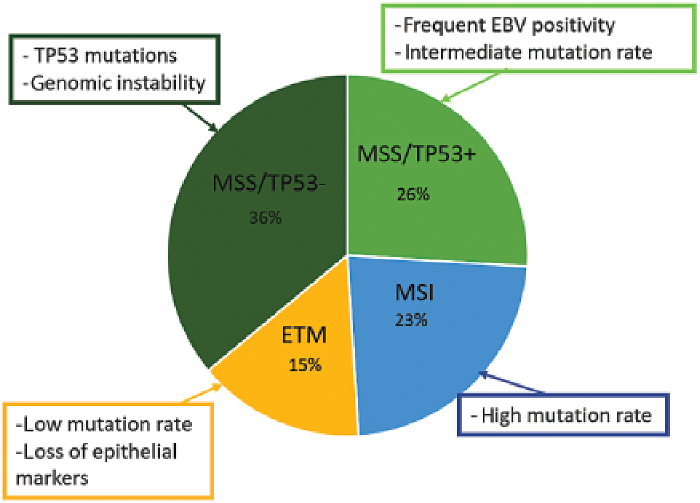


Figure 2 Subtype classification according to the Asian Cancer Research Group (ACRG) with percentage for the four subtypes: MSI (microsatellite instable), MSS/EMT (microsatellite stable/epithelial-to-mesenchymal transition), MSS/TP53+ (TP53 active) and MSS/TP53- (TP53 inactive) and molecular features in boxes (Adapted from (Rodriquenz et al. 2020)).

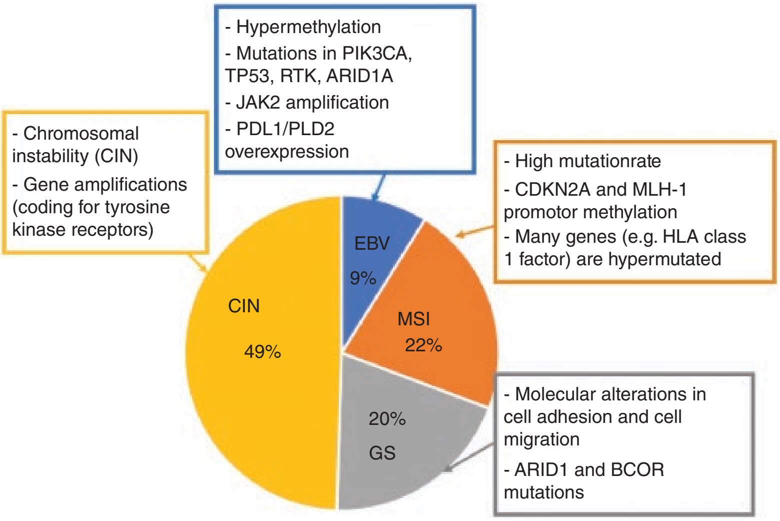


Figure 3 Subtype classification according to The Cancer Genome Atlas (TCGA) with percentage for the four subtypes: Epstein-Barr virus positive (EBV), microsatellite instable (MSI), genomically stable (GS) and chromosomal instability (CIN) and molecular features in corresponding boxes (Adapted from Rodriquenz et al. 2020).

3. Mutation Analyses for Differentiation between Diffuse Gastroesophageal Cancer (DGEC) and Intestinal Gastroesophageal Cancer (IGEC)

a) **NGS**: Next Generation Sequencing (NGS) has become the key technology for mutation analysis especially with samples of low tumor content. Since this technique is more widely available nowadays, it is also an important goal to determine its feasibility and reliability in comparison with IHC/FISH analyses of GECs. A study in 2015 demonstrated 84% concordance rate (Mikhail et al. 2015). Though several other attempts were undertaken to test the concordance, the results are still uncertain. Moreover, the identification on molecular mutation patterns is an ongoing process of improvement.

Whole genome sequencing (WES) made some important investigations for classification of diffuse and intestinal GECs. The analysis showed several somatic alterations in the *TP53*, β-catenin (CTNNB1), *CDH1* and the *RHOA* genes for the dGEC (Wang et al. 2014). Furthermore, the CDH1 mutation was mainly present in the dGEC and a gain of function in the RHOA protein was more often detected in the dGEC than in iGEC (Kakiuchi et al. 2014).

Activation of the phosphatidylinositol 3-kinase/AKT target (PIK3K-AKT) of the rapamycin pathway occurs via cell surface receptors as: Transcription activator STAT3, HER-2 and VEGFR2. This pathway contains several in the pathway included genes such as *PIK3A*, *PTEA*, *AKT3*, *AKT2*, and *AKT1*. Mutations in these genes are seen in a higher percentage of patients with dGEC.

Besides the differentiation of the two main histologic types, squamous cell carcinoma (SCC) and adenocarcinoma is also possible via genetic profiling with NGS, since both show distinct mutation patterns. Most driver mutations found in the adenocarcinoma are already present in the Barrett's esophagus and the one in the squamous dysplasia also in SCC. For example, more insertions and deletions as well as inactivating NOTCH1 mutations were found in SCC (Agrawal et al. 2012; Taylor et al. 2013).

b) **Germ-line Mutations**: One important germ-line mutation is in the cell–cell adhesion protein E-catherin (CDHI). Germline or somatic CDH1 mutations are typical in dGEC, since inactivation of CDH1 protein is associated with a hereditary dGEC and shorter survival rates in general (Cho et al. 2017). Here the signal pathways of E-cadherin, Wnt or RHOA are altered which enables cell adhesion and migration in GEC (Barber et al. 2008; Hansford et al. 2015).

c) **Gene Expression**: Additionally, to the classifications of the TCGA, using gene expression analyzes it was also possible to find molecular signatures that can be used as GEC classification criteria. Different gene expression patterns were proposed for the iGEC and dGEC. Here the iGEC revealed a concordance of 64% with Laurén histopathologic subtyping (Tan et al. 2011). Furthermore, a study group suggests that a classification into the subtypes proximal nondiffuse gastric cancer (more common Laurén's intestinal histology), diffuse gastric cancer (located in the body or distal stomach and Laurén's dGEC), and distal nondiffuse gastric cancer (iDGEC and mixed Lauren's histology) was possible (Shah et al. 2011). But genetic expression profiles are not only helpful tools for classification issues, but can also provide genes that are of prognostic importance or are associated with the likelihood of relapse (Cho et al. 2011). There are even genes as PIP5KL1 whose overexpression is correlated with suppression of GEC development (Shi et al. 2010). But also gene expression of certain genes as microRNAs can be used as a prognostic factor for the OS of GEC patients (Ueda et al. 2010).

d) **Microsatellite Stability and Copy Number Variations (CNV)**: The loss of heterozygosity (LOH) is ften associated with the intestinal or mixed GEC type, suggesting more genome instability in the iGEC type (Kim et al. 2003, Kwon et al. 2018). In the dGEC type less of somatic and germline mutations were found compared to the iGEC type. This indicates more genetic stability in the dGEC type (Wong et al. 2014). In dGEC also an increased gene amplification of the MDM2 gene and a gene fusion of the TSC2-RMF2016 genes were reported. Additionally, a gain in copy number variation in chromosome 13q was also a sign for the dGEC subtype (Wu et al. 2001).

e) **Epigenetic Alterations**: Epigenetic mechanisms include altered gene expression via DNA methylations and histone modifications without altering the genetic DNA sequence. Especially promotor hypermethylation causing transcriptional silencing of specific genes as tumor suppressor genes, which are a well-studied cause of cancer. But also silenced genes controlling the cell cycle, DNA repair mechanisms and cellular network or apoptosis are significant for carcinogenesis. The most common mechanism of gene silencing is the CpG island methylations, which can be used as a prognostic and predictive biomarker. Frequently hypermethylated and as such silenced genes in the GE cancer are for instance *CDK2NA, CDK2AP2, CDH1, MGMT, RASSF1, RUNx3*, and *DLC1* (Kim et al. 2004). Especially *Helicobacter pylori* and EBV cause a set of different hypermethylations that are associated with GE cancer (To et al. 2002). Even in early stages of gastric carcinogenesis aberrant methylation already accumulate and lead to premalignant lesions (Kang et al. 2003). Here the genome-wide search has identified one important methylation hotspot in GEC, the TFPI2 genes were highly methylated (about 81 (%) and this can be used as a prognostic indicator in GEC (Jee et al. 2009)).

Peritoneal Metastasis

Patients with peritoneal metastasis in GEC often develop as bowel obstruction and malignant ascites and have unsatisfactory response to chemotherapy and are associated with poor prognosis. All in all, about 55–60% of patients with GEC develop peritoneal metastases and the no targeted therapy or immunotherapy is available yet. Therefore, it is necessary to identify patients at high risk of peritoneal metastasis via molecular biomarkers. To find genes that are associated with peritoneal metastases, a group of researchers performed comprehensive whole-genome and transcriptome sequencing analysis of peritoneal metastasis from GEC. The found mutations are summarized in the Catalogue of Somatic Mutations in Cancer database and are also located in eight genes that were newly described in GEC (*ARMC4*, *CCDC178*, *DAB1*, *DMBT1*, *PDZD2*, *PLIN4*, *PKLR*, and *TUBB6*). Analysis of gene expression showed six genes (*CDH16*, *HOXA11*, *LOC100505875N*, *KX2*-5, *NOX4*, and *SFRP4*) which were up-regulated in the peritoneal metastasis in GEC (Zhang et al. 2015). In patients with peritoneal metastasis transcriptional profiling of miRNA was also performed. Here three miRNAs (miR-30a-5p, -659-3p, and -3917) were significantly overexpressed in patients with peritoneal metastasis in GEC, which correlates with the poor prognosis (Shimura et al. 2021). Therefore, the combination of this miRNA signature and the Bormann macroscopic type offers a potentially accurate approach for the detection of peritoneal metastasis in GEC (Yao et al. 2020).

B) Germline Genetics of Gastric and Esophageal Adenocarcinoma

1. Gastric Adenocarcinoma

A familial clustering of gastric adenocarcinoma, here called gastric cancer, is observed in 5–10% of all affected patients (Zanghieri et al. 1990). Besides common environmental factors, this implies that genetic factors are involved in disease development. Accordingly, twin studies have estimated a gastric cancer heritability of 28% (Lichtenstein et al. 2000). With the development of modern molecular genetic methods, the first genetic risk factors for gastric cancer could be identified respectively. This revealed that its genetic architecture is heterogeneous and depends on the effect size and frequency of the underlying genetic variants and mutations (Figure 4). Here, monogenic forms must be distinguished from multifactorial forms. Monogenic refers to mutations in a single gene, which have strong effect sizes and are extremely rare in the general population.

The only monogenic gastric cancer syndrome identified so far is hereditary diffuse gastric cancer (HDGC). It was first described in 1964 in three Maori families from New Zealand (Jones 1964) and is caused by mutations in the gene CDH1 (E-cadherin) that are inherited in an autosomal dominant fashion (Guilford et al. 1998). Gastric cancer also occurs in the context of other hereditary cancer syndromes (Table 1). However, other cancer types are predominant in these families. These include Lynch syndrome, Li-Fraumeni syndrome, familial adenomatous polyposis (FAP), harmatous polyposis syndromes (Peutz-Jeghers syndrome and juvenile polyposis), as well as hereditary breast and ovarian cancer (HBOC).

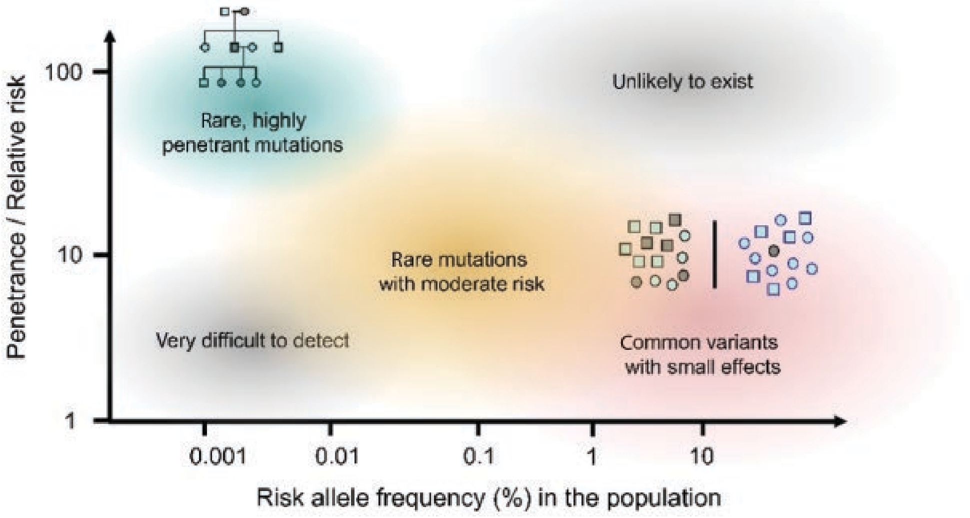

Unlikely to exist
Rare, highly penetrant mutations
Rare mutations with moderate risk
Very difficult to detect
Common variants with small effects
Penetrance / Relative risk
100
10
1
0.001
0.01
0.1
1
10
Risk allele frequency (%) in the population

Figure 4 The genetic architecture of diseases depends on the penetrance (Y-axis) and frequency of the risk-conferring mutation/variant in the population (X-axis). At the top left are monogenic diseases with extremely rare and highly penetrant mutations. Bottom right are multifactorial diseases with common risk variants that have small effects. In between are diseases with rare mutations that have moderate effects (adapted from (18398418)).

In contrast, the majority of all gastric cancers are multifactorial. Here, a large number of genetic variants is cumulatively involved in cancer development, which have only small effect sizes and are common in the general population (Figure 4). With the development of modern sequencing technologies or next generation sequencing (NGS) it has also become possible to identify gene variants that are rare in the general population and have moderate effect sizes (Figure 4). Additionally such risk variants for gastric cancer have recently been identified.

In the following, the different genetic forms of gastric cancer will be presented in more detail. Of all hereditary cancer syndromes listed in Table 1 this concerns HDGC, since gastric cancer is the predominant cancer type only in this syndrome.

a) **Hereditary Diffuse Gastric Cancer (HDGC)**: Histopathologically, HDGC presents as diffuse adenocarcinoma and shows an autosomal dominant inheritance (Gayther et al. 1998). However, because CDH1 mutations are not completely penetrant or can result as de novo mutations, a negative family history for diffuse gastric cancer does not exclude HDGC. In these cases, the age of onset is crucial for the diagnosis as HDGC is characterized by an early age of onset (Gayther et al. 1998). Accordingly, the majority of HDGC cases develop the disease before the age of 40 with an average age of onset of 38 years. However, the age of onset varies even among patients within a family (Gayther et al. 1998; Guilford et al. 1998).

The clinical presentation of HDGC does not differ from sporadic or multifactorial gastric cancer. In early stages symptoms are rather unspecific, but become characteristic in advanced disease stages (Wanebo et al. 1993). As with sporadic gastric cancer, the five-year survival rate of HDGC is 90% in early stages, whereas it is less than 20% in advanced stages (Oliveira et al. 2015). Thus, prophylactic gastroectomies are recommended for CDH1 mutation carriers.

As with other hereditary cancer syndromes, the penetrance of CDH1 mutations is incomplete. Data from large studies showed that around 67% of all male mutation carriers and around 83% of all female mutation carriers develop HDGC by the age of 80 (Pharoah et al. 2001). Moreover, female mutation carriers have also an increased risk for lobular breast cancer. Here, the prevalence is 39–52% and the average age of onset is 53 years (Pharoah et al. 2001). Thus, around 90% of all female mutation carriers will develop either gastric or breast cancer. Furthermore, it remains unknown whether colorectal cancer also occurs more frequently in patients with CDH1 mutations (Fitzgerald et al. 2010).

The clinical criteria for a CDH1 mutation analysis have been established by the International Gastric Cancer Linkage Consortium (IGCLC) (Pharoah et al. 2001) (Table 2). In addition to a detailed medical history of the index patient (including tumor histopathology), data from a three-generation pedigree should be considered. Depending on the

Table 1 Hereditary cancer syndromes with higher risk to develop gastric cancer (adapted from (van Nistelrooij et al. 2018)).

	Gastrointestinal cancer syndromes				**Multiorgan cancer syndromes**	
	Lynch syndrome (HNPCC)	**Familial adenomatous polyposis (FAP) (Jankowski et al. 1999)**	**Peutz-Jeghers syndrome**	**Juvenile polyposis**	**Hereditary Breast and Ovarian Cancer (HBOC)**	**Li-Fraumeni syndrome**
Gene(s)	DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS1, PMS2), EPCAM	APC	STK11	SMAD4, BMPR1A, ENG	BRCA1, BRCA2	TP53
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Predominant cancer type	Colorectal cancer	Colorectal cancer	Colorectal and gastric cancer, pancreatic cancer, breast and ovarian cancer	Colorectal and gastric cancer, pancreatic cancer	Breast and ovarian cancer	Broad cancer spectrum (including sarcomas, breast cancer, brain tumors)
Prevalence	1:370 to 1:2,000	1:8,300	1.9:1,000,000	1:100,000	1:400 to 1:500	1:20,0000
Gastric cancer risk	0.2–13%	2.1–4.2%	29%	21%	2.6–5.5%	3.1–4.9%

1 HNPCC = hereditary non-polyposis colon cancer
2 including GAPPS (gastric adenocarcinoma and proximal polyposis of the stomach)

inclusion criteria used for molecular genetic testing, the mutation detection rate in CDH1 is 30–50% (Oliveira et al. 2015). Accordingly, no CDH1 mutation is identified in 50–70% of all clinically defined HDGC cases. Here, it must be assumed that the mutations are localized in CDH1 regions that cannot be analyzed with the sequencing techniques available to date. Alternatively, so far unknown disease genes for HDGC might exist.

CDH1 on chromosome 16q22 consists of 16 exons and covers a genomic region of > 100 kb. The gene product represents a transmembrane protein that is - among others - involved in cell-cell adhesion processes (Oliveira et al. 2015). So far, more than 120 different CDH1 mutations have been identified in HDGC cases, the vast majority of them result in a truncated gene product at the protein level (Oliveira et al. 2015).

If a CDH1 mutation is detected in a patient with diffuse gastric cancer, a total gastrectomy is recommended unless alternative therapeutic procedures are more appropriate because of the disease stage or other clinical reasons. In

Table 2 Criteria for the diagnosis of HDGC according to the IGCLC guidelines (only one criterion must be fulfilled).

- **Family criteria (first or second degree relatives of each other)**
  - ≥ two cases of gastric cancer in family regardless of age, with at least one diffuse gastric cancer
  - ≥ 1 case of diffuse gastric cancer any age and ≥ 1 case of lobular breast cancer < 70 years in different family members
  - ≥ 2 cases of lobular breast cancer in family members < 50 years
- **Individual criteria**
  - Diffuse gastric cancer < 50 years
  - Diffuse gastric cancer at any age in individuals of Maori ethnicity
  - Diffuse gastric cancer at any age in individuals with a personal of family history (first degree) of cleft lip/cleft palate
  - History of diffuse gastric cancer and lobular breast cancer, both diagnosed < 70 years
  - Bilateral lobular breast cancer, diagnosed < 70 years
  - Gastric in situ signet ring cells and/or pagetoid spread (bottom to top) of signet ring cells in individuals < 50 years

addition, regular gynecologic and colonoscopic screenings are recommended for mutation carriers. Moreover, if a predictive diagnostic lead to the detection of a familial CDH1 mutation in healthy family members, a prophylactic gastrectomy is recommended from the age of 20 (Fitzgerald et al. 2010; Oliveira et al. 2013; Syngal et al. 2015).

b) Sporadic or Multifactorial Gastric Cancer: The majority of all gastric cancers is multifactorial. Here, single nucleotide polymorphisms (SNPs), which represent the most frequent class of common variants in the genome, contribute to disease development in a cumulative fashion (Figure 4). SNPs are characterized by the substitution of a single nucleotide and can be analyzed through genome-wide association studies (GWAS) since around 15 years. In GWAS, all common SNPs of the genome are systematically tested for disease association in large case-control cohorts. If an allele of a SNP is more frequent in patients than in controls and this difference exceeds a certain significance threshold, the variant is disease-associated.

In gastric cancer, seven GWAS in the Asian population and one GWAS in the European population have been carried out so far (Helgason et al. 2015; Hu et al. 2016; Jin et al. 2012; Sakamoto et al. 2008; Shi et al. 2011; Syngal et al. 2015; Wang et al. 2017; Yan et al. 2020). The size of the studied samples ranged from 937 to 2,240 patients (Abnet et al. 2010; Sakamoto et al. 2008). In total, 10 genomic loci could be identified that showed genome-wide significant association to gastric cancer. At present, for most of these loci it is rather unclear what genes and cellular mechanisms are involved in disease pathology. However, the functional characterization of the identified risk loci will be of major importance in future as this represents the prerequisite for developing novel and biologically based therapy and prevention strategies. At one locus, however, the cellular pathomechanism is already known. It involves the gene ATM (ataxia telangiectasia mutated) on chromosome 11q22, which encodes a serine-protein kinase involved in the repair of DNA double-strand breaks. The ATM variants that showed disease association (Helgason et al. 2015) are located in the coding region and lead to a premature termination of the protein. The risk SNPs are also relatively rare in the general population (< 1%) and compared to most GWAS show relatively strong effect sizes (odds ratio (OR) > 4). Therefore, many scientists consider ATM to be rather a moderately penetrant disease gene for gastric cancer (see following section) then a multifactorial risk gene.

c) Moderately Penetrant Disease Genes for Gastric Cancer: In recent years, NGS or whole-exome sequencing (WES) has led to the identification of the first disease genes for gastric cancer with moderate effect sizes (Figure 4). The largest of these studies represents The Cancer Genome Atlas (TCGA) consortium study, which analyzed 33 different cancer types, including WES data from 443 patients with gastric cancer (Huang et al. 2018). Overall, pathogenic or likely pathogenic mutations in various genes could be identified in 13% of all patients. Surprisingly, the age of onset was 61 years in the group of mutation carriers and thus not significantly lower than in the overall cohort. Mutations were found significantly frequently in two tumor suppressor genes, namely PALB2 (partner and localizer of BRCA2) on chromosome 16p12 and ATM on chromosome 11q22 (see above). In both genes mutations were present in patients with both intestinal and diffuse gastric cancer. PALB2 mutations were also identified among patients with other cancer types, but showed no significant enrichment in these cases. In contrast, mutations in ATM were also observed significantly frequently in patients with breast, lung, pancreas, and prostate cancer.

Other NGS-based studies primarily analyzed CDH1-negative patients with diffuse gastric cancer, some of whom met the clinical HDGC criteria. The size of the study cohorts ranged from 22 to 183 patients (Gaston et al. 2014; Hansford et al. 2015; Majewski et al. 2013). Although pathogenic mutations in the gene CTNNA1 (catenin alpha 1) on chromosome 5q31 were found in some cases, no significant enrichment of mutations was observed (Reid et al. 2010). However, CTNNA1 interacts at the cellular level with CDH1, the disease gene for HDGC. This can be considered as further evidence that CTNNA1 is a disease gene for diffuse gastric cancer.

2. Esophageal Adenocarcinoma

Also in esophageal adenocarcinoma, here called esophageal cancer or Barrett's carcinoma, genetic factors are involved in disease development. Accordingly, the heritability estimates range from 30–40% (Reid et al. 2010). However, as with gastric cancer, a spectrum of genetic risk factors appears to contribute to esophageal cancer. The majority of these cases are sporadic and of multifactorial etiology. Here, a large number of common genetic variants, each with small effect size, contribute cumulatively to disease risk (Figure 4). In contrast, esophageal cancer and its precursor lesion Barrett's esophagus do not appear sporadically in some patients. This is called familial Barrett's esophagus/carcinoma, which affects about 7% of cases, and is defined by three or more affected relatives (To et al. 2016). In these patients, it is assumed that gene variants, which are rare in the general population and have moderate effect sizes, are contributed to disease risk (Figure 4). However, in contrast to gastric cancer, esophageal cancer does not develop in the context of a monogenic or hereditary tumor syndrome.

a) Sporadic or Multifactorial Esophageal Cancer: In 2016, a GWAS meta-analysis was published that jointly analyzed all previous GWAS cohorts (Gharahkhani et al. 2016; Su et al. 2012). The sample comprised of > 6,000 patients with Barrett's esophagus, > 4,000 patients with Barrett's carcinoma and

> 17,000 controls, all of European descent. In total, 14 risk loci for Barrett's esophagus/carcinoma were identified by this GWAS. Of note, one of these loci is located on chromosome 3q27 (SNP rs9823696) and was associated specifically with Barrett's carcinoma ($p = 1.6 \times 10^{-08}$), but not with Barrett's esophagus ($p = 0.45$). On the single marker level, this genetic variant represents the first variant that predicts the progression from Barrett's esophagus to esophageal cancer. However, through increasing GWAS sample sizes further genetic risk and progression factors will be identified in future. The GWAS data also revealed that sex-specific genetic effects are involved in the development of Barrett's esophagus/carcinoma (Dong et al. 2013). Accordingly, one SNP on chromosome 6q11 (rs112894788) showed disease-association only in males, whereas one SNP on chromosome 8p23 (rs13259457) showed disease-association only in females. For most of the identified GWAS loci it is rather unclear what genes and cellular mechanisms are involved in disease pathology. However, their functional characterization will be of major importance in future for the development of novel and biologically based therapy and prevention strategies.

b) Moderately Penetrant Disease Genes for Esophageal Cancer: Familial Barrett's esophagus/carcinoma affects about 7% of cases and is defined by three or more affected relatives (To et al. 2016). In addition to the familial clustering, an earlier age at onset has been observed in these cases when compared with sporadic forms (To et al. 2016). Examples of published reports of familial Barrett's esophagus/carcinoma are listed in Table 3.

It is assumed that gene variants, which are rare in the general population and have moderate effect sizes, are contributing to familial Barrett's esophagus/carcinoma (Figure 1). Accordingly, first WES studies have been carried out on single families with several affected individuals. This led to the identification of the gene VSIG10L (V-set and immunoglobulin domain containing 10 like) on chromosome 19q13, where the mutation p.S631G segregated with disease status in a family (Fecteau et al. 2016). Furthermore, the mutation p.V120G in the gene MSX1 (Msh homeobox 1) on chromosome 4p16 segregated with disease status in another pedigree with familial Barrett's esophagus/carcinoma (van Nistelrooij et al. 2018). In the pre-WES era, the gene MSR1 (Macrophage scavenger receptor 1) on chromosome 8p22 was identified as another potential disease gene for familial Barrett's esophagus/carcinoma (with the mutations p.R293X and p.L254V). In this study, a linkage analysis was performed on 21 concordant-affected sib-pairs and 11 discordant sib-pairs. Subsequently, genes in linkage regions were sequenced in 176 further patients and 200 controls (To et al. 2016). However, the relevance of the mentioned genes for esophageal cancer development has so far not been confirmed by studies on independent cases.

C) Pathology of Esophageal and Gastric Adenocarcinoma

1. General Differences

Cancer of the distal esophagus and stomach share a lot of the histological criteria when to diagnose neoplasia. Both entities are adenocarcinomas whereas esophageal cancer on normal is a squamous cell carcinoma with different criteria, etiology, and

Table 3 Selection of published case reports and case series on familial Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) ordered according the number of included patients. The average age at diagnosis (AAD) is listed for BE and EAC. In all studies, the observed inheritance pattern was autosomal dominant (AD) (adapted from (To et al. 2016)).

References	Families (n)	BE (n)	EAC (n)	Mean BE AAD	Mean EAC AAD	Inheritance
(Drovdlic et al. 2003)	70	21	2	51.0	60.5	AD
(Sappati Biyyani et al. 2007)	20	7	7	60.3	60.8	AD
(Poynton et al. 1996)	3	6	8	62.0	60.0	AD
(Fahmy and King 1993)	4	8	2	62.0	74.0	AD
(Groves et al. 2005)	1	7	3	48.1	74.0	AD
(Munitiz et al. 2008)	1	4	6	46.2	60.5	AD
(Jochem et al. 1992)	1	6	3	43.6	74.0	AD
(Eng et al. 1993)	1	7	2	54.3	68.0	AD
(Crabb et al. 1985)	1	4	0	59.5	-	AD
(Everhart et al. 1983)	1	3	0	23.6	-	AD
(Melzer et al. 2006)	1	0	3	-	65.5	AD

molecular background. Squamous cell carcinomas of the esophagus are etiologically linked to alcohol and tobacco consumption but also chronic inflammatory conditions like Lichen planus can be seen as a precancerous condition.

Dysplasia is thought to be the first visible step of malignant transformation in the gastro-intestinal tract. The term dysplasia was first used by E. Krompecher, Budapest in 1924 (Krompecher 1924) describing cells that look abnormal under a microscope but are not yet cancer. In fact, we have no better description nowadays and all our attempts for a better risk stratification in subgrading dysplasia in low and high grade cases are partly very subjective since criteria are still ill-defined and there may be a considerable overlap between the stages (Figures 5 and 6).

Carcinomas of the distal esophagus are adenocarcinomas most often based on metaplastic changes of the squamous epithelium into columnar epithelium based on chronic damage due to gastro-esophageal reflux disease called Barrett's esophagus (esophagitis-metaplasia-dysplasia-adenocarcinoma sequence) (3). Gastric carcinomas are mainly based on chronic active inflammation due to infection with *Helicobacter pylori*. Therefore, the WHO is regarding Helicobacter as a category I carcinogen. It is also a good example that antibiotic treatment has the potential to cure a precancerous condition. In case of low grade gastric MALT Lymphoma which is Helicobacter-induced in most cases, antibiotic treatment is even capable to cure a malignant disease.

Concerning the aggressiveness of cancer, squamous cell carcinoma is more aggressive than Barrett's associated adenocarcinoma and gastric adenocarcinoma. The rate of lymph node metastasis is higher in squamous cell carcinoma compared with adenocarcinoma. This is the reason that the depth of infiltration still acceptable for local endoscopic removal/ablation should not exceed 200 microns into the submucosal layer for squamous cancer (Figure 7) and 500 microns for Barrett's adenocarcinoma or gastric adenocarcinoma (Figure 8). In comparison colonic carcinoma is even less aggressive then gastric adenocarcinoma and thus the border for endoscopic removal in the colon is 1000 microns into the submucosal layer, in case there are no further risk factors such as lymphatic vessel permeation, poor differentiation or high budding (single tumor cells at the invasive front).

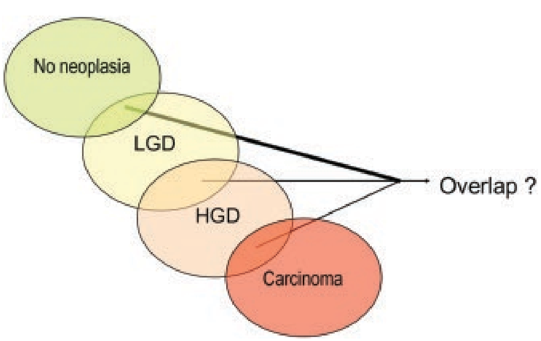


Figure 5 Steps in the cascade of malignant transformation with overlaps. It has to be noted that the time one stage takes to the next stage up may vary considerably in length and in some cases it even looks like whether stages are so short in time that lesions advance very fast. It is not foreseeable at the moment which neoplasm will behave more or less aggressive. This is the reason why cases with dysplasia should not be watched but removed today. (LGD = low grade dysplasia; HGD = high grade dysplasia).

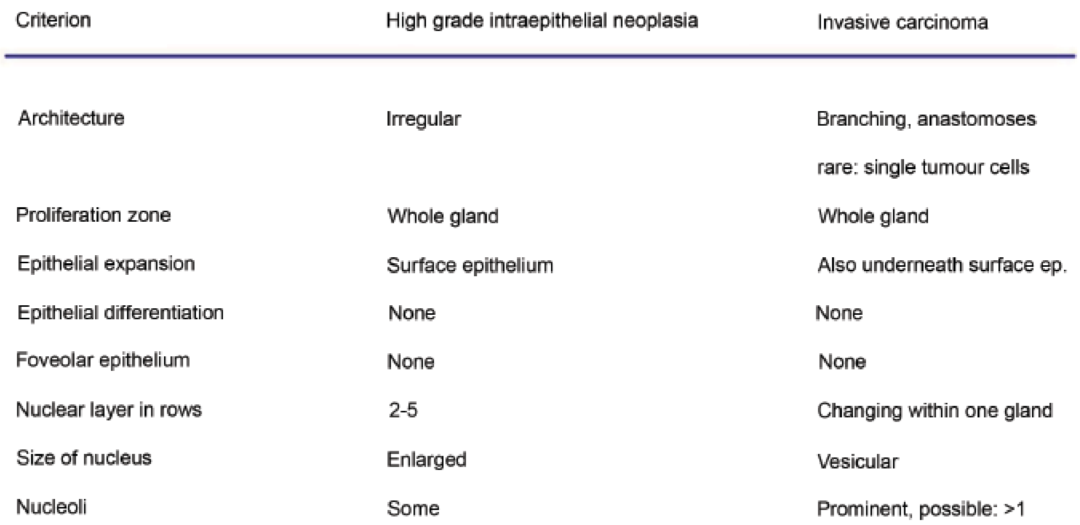
2. Diagnostic Dilemma

Besides squamous cell neoplasia, diagnostic criteria for neoplasia of columnar mucosa are partly ill defined, non-validated, nor are they accepted worldwide. These criteria vary internationally and institutionally depending on the place where people have been trained. This is the reason for a lower carcinoma threshold in Japan and a higher threshold for a carcinoma diagnosis in the United States. Europe is located somewhere in between. Pathologists' abilities are different but not poor. In their differences all the colleagues are very consistent and can even predict that a certain lesion diagnosed in Japan would be called carcinoma whereas the colleagues in the United States would prefer the diagnosis of high-grade dysplasia/intraepithelial neoplasia.

It has been shown during the Vienna consensus that the differences are mainly found in biopsies but not in resection specimen (Figures 9 and 10).

A carcinoma diagnosis in Japan is mostly based on the cytology of the epithelial cells whereas in Western countries architecture and secondary effects like desmoplastic stromal reaction or single tumor cells play an important diagnostic role. It is known that desmoplastic stromal reaction can be detected in deeply submucosal tumors but not in early mucosal carcinomas. Also, well differentiated adenocarcinomas are capable of building their own basal membrane and thus no single tumor cells can be expected in early carcinomas. The diagnostic dilemma is that it is not clear who is wrong or who is right. The ultimate proof would be the presence of vessel or perineural permeations or metastases. Unfortunately, these sequels of a carcinoma may not be present in early lesions.

Colleagues (Sakurai et al. 2014) from Japan were able to document these issues by asking Japanese and Western pathologists to make a biopsy diagnosis and a final diagnosis on the resection specimen of the same lesion. It turned out that Western pathologists tended to diagnose clear cut submucosal cancer as high grade dysplasia and signed out cases with additional vessel permeations as high grade dysplasia in biopsies as well. On the resection specimen the Japanese and Western pathologists all agreed upon the carcinoma diagnosis. Due to the different medical systems and the different history of the evolvement of these systems, there is an alternative for both sides to overcome these issues on biopsy specimen. Takahashi



Criterion	High grade intraepithelial neoplasia	Invasive carcinoma
Architecture	Irregular	Branching, anastomoses rare: single tumour cells
Proliferation zone	Whole gland	Whole gland
Epithelial expansion	Surface epithelium	Also underneath surface ep.
Epithelial differentiation	None	None
Foveolar epithelium	None	None
Nuclear layer in rows	2-5	Changing within one gland
Size of nucleus	Enlarged	Vesicular
Nucleoli	Some	Prominent, possible: >1

Figure 6 Criteria for differentiating High grade intraepithelial neoplasia/dysplasia from invasive carcinoma within the gastrointestinal tract. Most important is the epithelial expansion underneath the surface to diagnose cancer in combination with malignant cytology (Vieth and Stolte 2005/ Springer Nature).

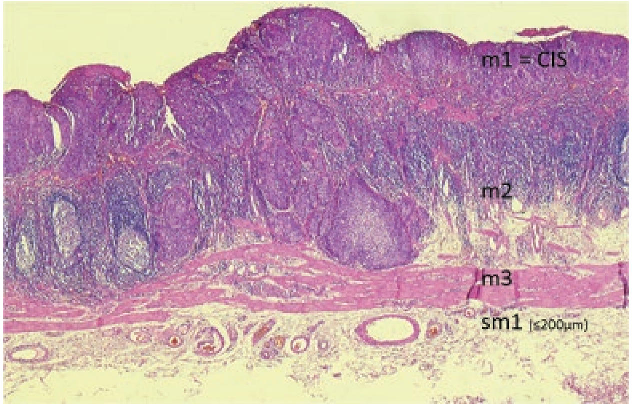


Figure 7 Esophageal m2 squamous cell carcinoma invading the tunica propria, reaching the muscularis mucosae but without invasion of the muscle layer. The upper third of the submucosal layer is defined as a depth of invasion less than 200 microns (CIS: carcinoma in situ).

and Iwama (Takahashi and Iwama 1985) evaluated the expansion patterns of neoplasia within the gastro-intestinal tract, independently with different approaches. In the end, the earliest sign of invasion is the so-called lateral expansion of tubules or intertubular fusions that are believed to represent nothing else but invasion into the tunica propria. (Figures 11–12).

In an unpublished series we were able to show with a Japanese colleague that lateral expansion plus cytology is a very strong marker for a carcinoma diagnosis and works on biopsies and resection specimens as well. There was 100% concordance with the Japanese cytological criteria of a carcinoma diagnosis. At this very moment one can state that the lateral

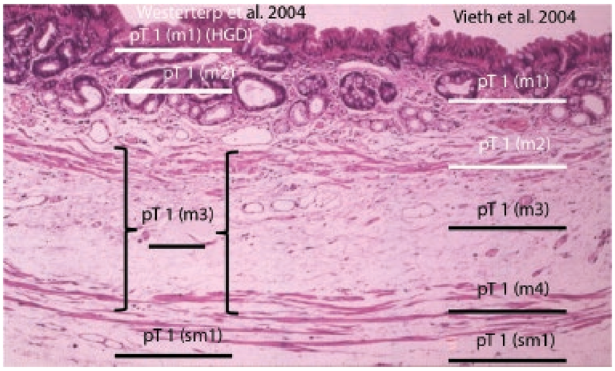
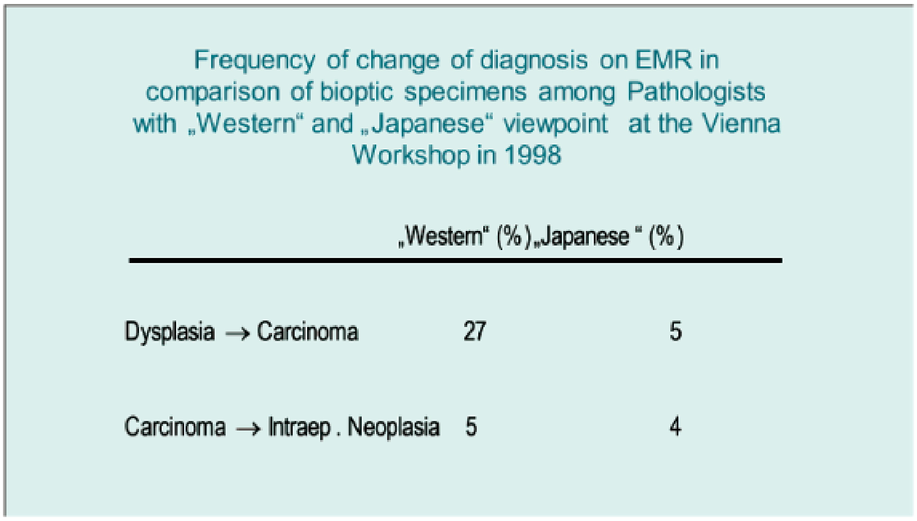


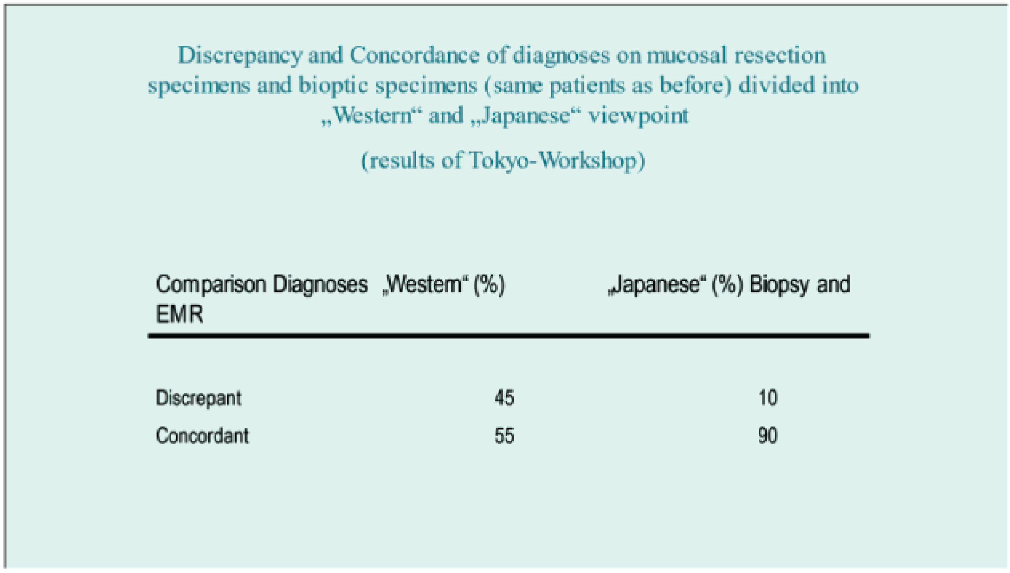
Figure 8 Barrett's mucosa with characteristic double muscularis mucosa (a probably reactive sequel of chronic inflammation). There are two proposals available. Unfortunately, studies often never state what system is used and this harbors a lot of issues in respect of interpreting results. The m1-m3 proposal (Westerterp et al. 2005) needs to be seen as an attempt to harmonize squamous and columnar epithelial neoplasia. Unfortunately, this means that HGD (high grade dysplasia) is now called an m1 carcinoma, m2 means a carcinoma that is confined to the upper mucosal lamina propria and m3 invasion of the upper layer of the muscularis, the space in between and the lower layer of muscularis mucosae. The upper third of the submucosal layer is defined as less than 500 microns. The competing proposal (Vieth and Stolte 2005) is based on the anatomical structures. Here, high grade dysplasia still exists as an entity, m1 names a carcinoma that is confined to the upper mucosal level, m2 invasion into the upper muscularis mucosae, m3 into the layer in between the muscle layers, and m4 invasion into the lower muscularis mucosae. One or the other system should be used to force the pathologists to clearly identify layers and to avoid of overdiagnosing an m3 carcinoma as being submucosal since this would have major therapeutic consequences compared to a lesion that is eligible for local endoscopic ablation.



Frequency of change of diagnosis on EMR in comparison of bioptic specimens among Pathologists with „Western“ and „Japanese“ viewpoint at the Vienna Workshop in 1998

	„Western“ (%)	„Japanese“ (%)
Dysplasia → Carcinoma	27	5
Carcinoma → Intraep. Neoplasia	5	4

Figure 9 (Adapted from (Schlemper et al. 1997)) Showing percentage of diagnostic up and downgrades between biopsy and later resection specimen diagnosis.



Discrepancy and Concordance of diagnoses on mucosal resection specimens and bioptic specimens (same patients as before) divided into „Western“ and „Japanese“ viewpoint

(results of Tokyo-Workshop)

Comparison Diagnoses EMR	„Western“ (%)	„Japanese“ (%) Biopsy and
Discrepant	45	10
Concordant	55	90

Figure 10 (Adapted from (Schlemper et al. 2001)) Discrepancies between biopsy diagnosis and resection specimen diagnosis.

expansion maybe a non-necessary criterion. This is true, indeed but it may help to bridge and overcome the differences in a constructive rather than an destructive way. The Western standpoint is that Japanese colleagues “overdo” the carcinoma diagnoses leading to a good prognosis and high incidences of “gastric carcinoma,” a proportion of which may not have become invasive for many years if at all, This standpoint, however, overlooks the subsequent rare differences between a biopsy diagnosis and the final diagnosis on the resection specimen in Japan. There is very strong evidence that when more biopsies, or sections are taken (>5), and when more expert pathologists (>2) are involved, in the patients diagnosis the accurary increases to the very best global standards in all stages of the esophagitis-metaplasia-dysplasia-adenocarcinoma sequence (Bennett et al. 2015).

3. Gastric Differentiation

In general, most columnar neoplasms of the upper gastrointestinal tract show an intestinal differentiation. This means they share a lot in common with tubular adenomas of the colon: hyperchromatic,

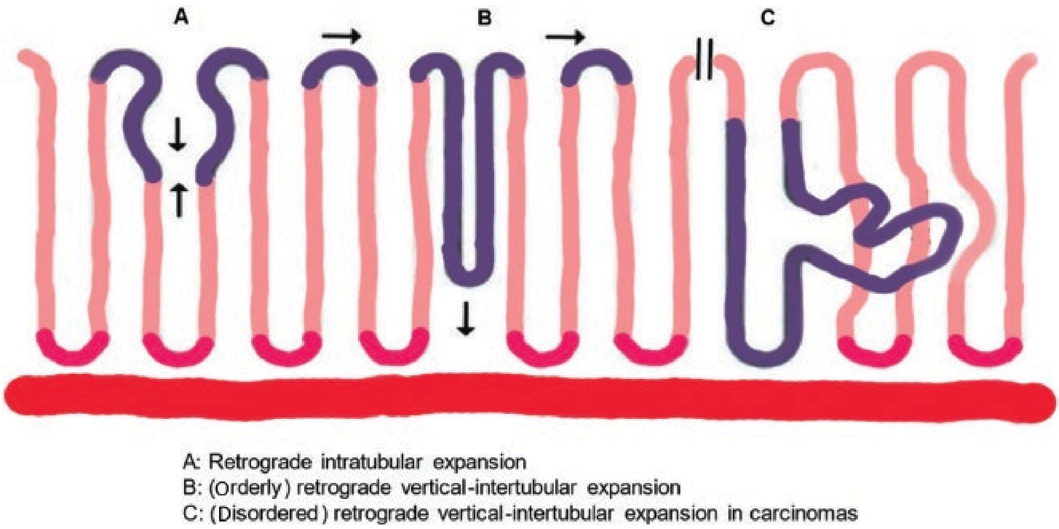

A
B
C
A: Retrograde intratubular expansion
B: (Orderly) retrograde vertical-intertubular expansion
C: (Disordered) retrograde vertical-intertubular expansion in carcinomas

Figure 11 (Adapted after (Borchard et al. 2000)) Expansion patterns from A retrograde intratubular and horizontal expansion along the surface in adenomas and later B retrograde vertical expansion by increased proliferation to C disordered vertical lateral expansion of invasive carcinomas.

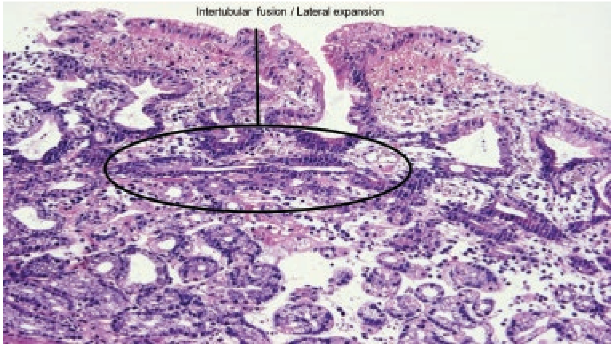


Figure 12 H&E of lateral expansion underneath the surface in as the earliest sign of invasion into the adjacent lamina propria in tubular well differentiated gastric adenocarcinoma.

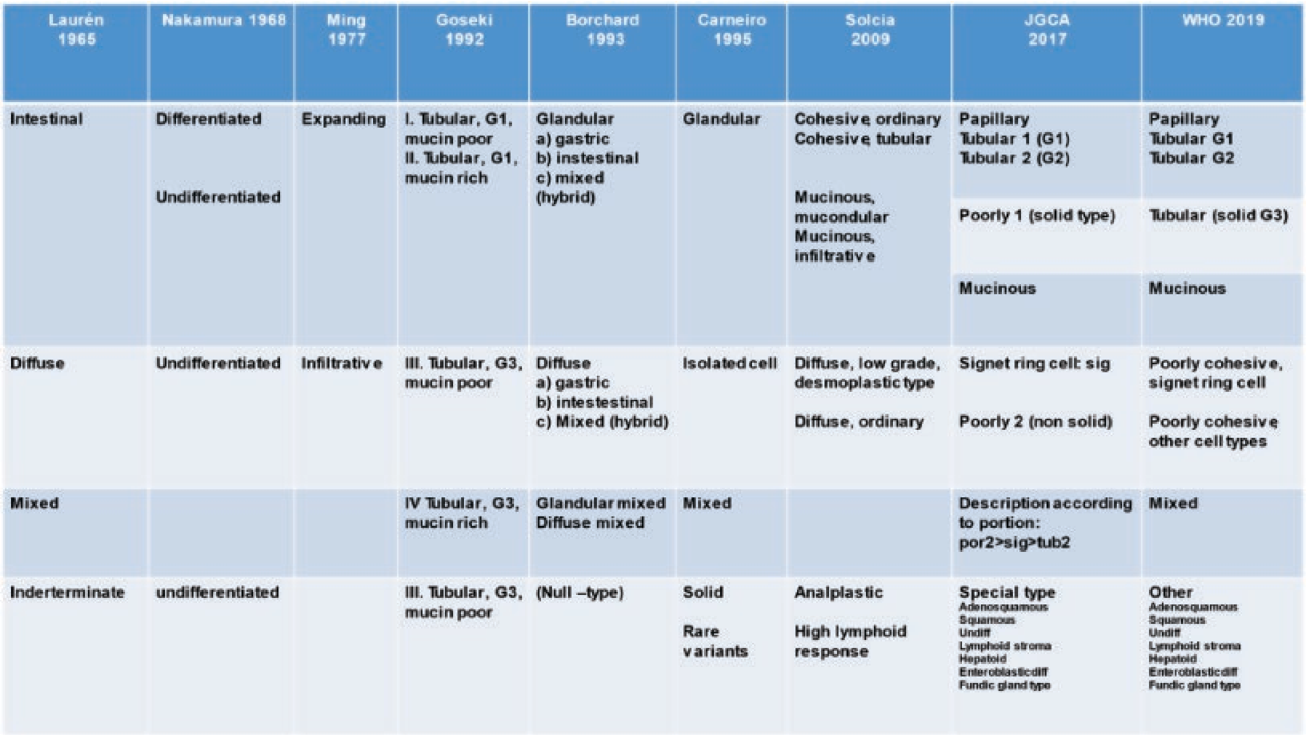
enlarged and palisading nuclei of the epithelium in case of low grade dysplasia. In high grade dysplasia the nuclei become round and leave their basal orientation and can build up so called cushions of up to 3–5 nuclei on top of each other within in the epithelium. In case of transition to carcinoma the afore mentioned lateral expansion can be seen.

This is different in cases where the neoplasms derive from deep gastric glands (pyloric glands) and lead to so called pyloric gland adenomas. The cytology is completely different in such cases. The cytoplasm is pale eosinophilic, nuclei are basal orientated but slightly elevated and show a round shape. The glands are densely packed and mimic a strange hyperplastic architecture as Elster (Elster 1976) noted in 1967 without knowing that he probably described and depicted the first pyloric gland adenoma in the literature. Besides the bland-looking cytology ca 30% of such lesions harbor transition to a carcinoma at the first diagnosis (Vieth et al. 2003). Such areas are sometimes hard to identify and the proliferation index may be of help in these cases since it is quiet low in pyloric gland adenoma with no higher grade of neoplasia.

Gastric surface epithelium can give rise to neoplasms as well. Then these neoplasms show a foveolar differentiation with small epithelial cells, cuboidal nuclei that are hyperchromatic. Abrupt transitions to the adjacent non neoplastic epithelium indicate the borders of the lesion. Characteristically these lesions show so-called apical mucin caps.

Mixtures between different gastric differentiations can be seen especially in Barrett's (Vieth et al. 2016) and in patients with syndromatic polyposis (Hackeng et al. 2017).

Furthermore, neoplasia can arise from chief cells and lead to so-called chief cell adenoma (Müller-Höcker and Rellecke 2003) which show typically a very suspicious architecture with marked lateral expansion. Fortunately, these lesions almost never metastasize and invade the submucosal layer infrequently. Unfortunately, there is an ongoing discussion of the dignity of such lesions. Most Western authors conclude by the low risk for metastasis that chief cell adenomas are benign lesions per se whereas Japanese authors per se make a carcinoma diagnosis based on cytology (and architecture). Probably the Japanese colleagues are correct and at least it is consistent with general criteria for a carcinoma diagnosis. The fact that pyloric gland adenoma also share features with chief cell adenomas (Kushima et al. 2013) but don't harbor parietal cells and show a different architecture that led to the idea to see pyloric gland adenomas and chief cell adenomas as two branches of a common progenitor cell. It is further complicated that chief cell adenomas are synonymously called oxyntic gland adenomas or fundic gland adenomas/carcinomas. Theoretically, this



Laurén 1965	Nakamura 1968	Ming 1977	Goseki 1992	Borchard 1993	Carneiro 1995	Solcia 2009	JGCA 2017	WHO 2019
Intestinal	Differentiated	Expanding	I. Tubular, G1, mucin poor II. Tubular, G1, mucin rich	Glandular a) gastric b) instestinal c) mixed (hybrid)	Glandular	Cohesive, ordinary Cohesive, tubular	Papillary Tubular 1 (G1) Tubular 2 (G2)	Papillary Tubular G1 Tubular G2
	Undifferentiated					Mucinous, mucondular Mucinous, infiltrative	Poorly 1 (solid type)	Tubular (solid G3)
							Mucinous	Mucinous
Diffuse	Undifferentiated	Infiltrative	III. Tubular, G3, mucin poor	Diffuse a) gastric b) intestestinal c) Mixed (hybrid)	Isolated cell	Diffuse, low grade, desmoplastic type Diffuse, ordinary	Signet ring cell: sig Poorly 2 (non solid)	Poorly cohesive, signet ring cell Poorly cohesive, other cell types
Mixed			IV Tubular, G3, mucin rich	Glandular mixed Diffuse mixed	Mixed		Description according to portion: por2>sig>tub2	Mixed
Inderterminate	undifferentiated		III. Tubular, G3, mucin poor	(Null –type)	Solid Rare variants	Analplastic High lymphoid response	Special type Adenosquamous Squamous Undiff Lymphoid stroma Hepatoid Enteroblasticdiff Fundic gland type	Other Adenosquamous Squamous Undiff Lymphoid stroma Hepatoid Enteroblasticdiff Fundic gland type

Figure 13 (Adapted after (Kushima et al. 2013)) Classification of gastric carcinomas over decades. Today including most variants and growth patterns. It is obvious that Laurén classification is not up to date anymore even it helped surgeons to determine the distance of safety margins for preventing relapses as marker for the aggressiveness of a tumor.

includes pyloric gland adenomas since they mostly develop in oxyntic mucosa as well. It is foreseeable that the terminology for pyloric gland/chief cell/fundic gland/oxyntic gland (Ushiku et al. 2020) needs to be adapted in the future to a more logical and uniform approach.

4. Classification of Gastric Carcinomas

For decades most pathologists worldwide stuck to the so-called Laurén classification with two alternatives how to classify gastric carcinomas namely into an intestinal type and a diffuse type. The reason was that this indicated the surgeons how far the resection margin needed to be. It was known that diffuse type of cancer has a worse prognosis and needed more aggressive options of treatment when advanced compared to intestinal type of cancer. Many shortcomings are associated with this classification namely also that "intestinal" and "diffuse" are not real opposites. The Japan Gastric cancer society early tried to overcome these issues by introducing updated versions by various authors taken the general growth pattern more detailed into account. Finally the WHO recognized these attempts and also proposed in the 2019 edition of gastrointestinal tumor classification (Digestive System Tumours WHO Classification of Tumours 2019) the use of the recent Japanese classification with mild terminology changes (Figure 13). This was a great step in the worldwide harmonization process since obviously comparison of studies was not properly possible anymore. It is possible to use the new terminology and old terminology in diagnostic pathology if clinicians want to stick to a certain terminology for their patients. Such further terminology can be given in brackets, easily.

One issue remaining with the increasing number of Helicobacter eradication therapies and the decreasing frequency of Helicobacter infected individuals is that we can see strange effects such as positive Helicobacter stool tests in individuals after successful eradication therapy and non-inflamed stomach. It turned out that there may be other Helicobacter infected areas in the GI-tract that can harbor a Helicobacter infection such as the bile ducts and especially the gallbladder. The meaning of such findings is still unclear. One can speculate if Helicobacter bacteria in the gallbladder may contribute to inflammation or malignant transformation within the gallbladder (Backert et al. 2018). Another sequel is the findings of precancerous lesions such as adenomas within non inflamed Helicobacter negative stomachs (Bertz et al. 2021).

Interestingly the rare foveolar adenomas are nowadays seen more often than in previous decades with high frequencies of Helicobacter infections. Even carcinomas are now detected in Helicobacter negative stomachs that have not been detected in earlier times. One can hypothesize two scenarios: a point of no return has been crossed prior to a successful Helicobacter eradication therapy. Cases developing gastric cancer after cure of

MALT Lymphoma by eradication therapy point into this direction (Rentien et al. 2018). This may explain some but not all of such cases since there are for sure Helicobacter naiive stomachs seen with gastric neoplasia (adenoma and carcinoma) and here it may be speculated that other triggers initiated malignant transformation (e.g. other infective agents then Helicobacter and/or environmental causes). Further research needs to clarify these issues to develop proper screening and early detection in those with higher risk for malignant transformation.

In conclusion there is major progress in the diagnostic, prognostic, and predictive biomarkers in the management of both esophageal and gastric cancer. The next decade will see the implementation of increasing holistic tissue molecular pathology profiles at all stages to act as an adjunct to classical histopathological diagnosis.

Key Take Home Messages

1 Esophageal squamous cancer is more rapidly invasive than esophageal and gastric adenocarcinoma.
2 The molecular genotype/phenotypes of esophageal cancers can predict response to therapy.
3 The more specialist pathologists involved in the diagnosis the greater the accuracy (>2).
4 The samples takes by biopsy or sampled in the resection the greater the accurarcy.

Areas for Further Research

1 There is insufficient data on circulating diagnostic biomarkers for esophageal cancer risk and development.
2 The best prognostic biomarkers are unknown.

Trusted Websites for Further Reading

https://jhu.pure.elsevier.com/en/publications/molecular-evolution-of-the-metaplasia-dysplasia-adenocarcinoma-se-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5538857
https://cancersearch.org/condition/barrett-adenocarcinoma~c/#.details

References

Abnet, C.C., Freedman, N.D., Hu, N. et al. (2010 September). A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nat Genet* 42 (9): 764–767. doi: 10.1038/ng.649. Epub 2010 Aug 22. PMID: 20729852; PMCID: PMC2947317.

Agrawal, N., Jiao, Y., Bettegowda, C. et al. (2012 October). Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. *Cancer Discov* 2 (10): 899–905. doi: 10.1158/2159-8290.CD-12-0189. Epub 2012 Aug 9. PMID: 22877736; PMCID: PMC3473124.

Backert, S., Tegtmeyer, N., Oyarzabal, O.A. et al. (2018 June 21). Unusual Manifestation of Live *Staphylococcus saprophyticus*, *Corynebacterium urinapleomorphum*, and *Helicobacter pylori* in the Gallbladder with Cholecystitis. *Int J Mol Sci* 19 (7): 1826. doi: 10.3390/ijms19071826. PMID: 29933576; PMCID: PMC6073424.

Barber, M., Murrell, A., Ito, Y. et al. (2008 November). Mechanisms and sequelae of E-cadherin silencing in hereditary diffuse gastric cancer. *J Pathol* 216 (3): 295–306. doi: 10.1002/path.2426. PMID: 18788075.

Bartley, A.N., Washington, M.K., Ventura, C.B. et al. (2016 December). HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the college of American pathologists, American society for clinical pathology, and American society of clinical oncology. *Am J Clin Pathol*. 146 (6): 647–669. doi: 10.1093/ajcp/aqw206. Epub 2016 Nov 14. PMID: 28077399; PMCID: PMC6272805.

Bennett, C., Moayyedi, P., Corley, D.A. et al. (2015 May). BOB CAT Consortium. BOB CAT: a large-scale review and delphi consensus for management of Barrett's Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia. *Am J Gastroenterol* 110 (5): 662–682.

Bertz, S., Angeloni, M., Drgac, J. et al. (2021 January 5). Helicobacter infection and gastric adenoma. *Microorganisms* 9 (1): 108. doi: 10.3390/microorganisms9010108. PMID: 33466325; PMCID: PMC7824786.

Blair, V.R., McLeod, M., Carneiro, F. et al. (2020 August). Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 21 (8): e386–e397. doi: 10.1016/S1470-2045(20)30219-9. PMID: 32758476; PMCID: PMC7116190.

Borchard F. Formen und Nomenklatur der gastrointestinalen Epithelexpansion: Was ist Invasion? [Forms and nomenclature of gastrointestinal epithelial expansion: what is invasion?]. Verh Dtsch Ges Pathol. 2000;84:50-61. German. PMID: 11217449.

Cancer Genome Atlas Research Network (2014). Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 513: 202–209.

Carneiro, F., Fukayama, M., Grabsch, H.I., and Yasui, W. (2019). *Gastric adenocarcinoma in the book: digestive system tumors: WHO classification of tumors editorial board in 5th Edition*. Chapter 3: 85–95.

Cecchi, F., Rabe, D.C., and Bottaro, D.P. (2012 June). Targeting the HGF/Met signaling pathway in cancer therapy. *Expert Opin Ther Targets* 16 (6): 553–572. doi: 10.1517/14728222.2012.680957. Epub 2012 Apr 25. PMID: 22530990; PMCID: PMC3711667.

Cho, J.Y., Lim, J.Y., Cheong, J.H. et al. (2011 April 1). Gene expression signature-based prognostic risk score in gastric cancer. *Clin Cancer Res* 17 (7): 1850–1857. doi: 10.1158/1078-0432.CCR-10-2180. Epub 2011 Mar 29. PMID: 21447720; PMCID: PMC3078023.

Cho, S.Y., Park, J.W., Liu, Y. et al. (2017). Sporadic Early-Onset Di_use gastric cancers have high frequency of somatic CDH1 alterations, but low frequency of somatic RHOA mutations compared with late-onset cancers. *Gastroenterology* 153: 536–549.

Crabb, D.W., Berk, M.A., Hall, T.R. et al. (1985 July). Familial gastroesophageal reflux and development of Barrett's esophagus. *Ann Intern Med* 103 (1): 52–54. doi: 10.7326/0003-4819-103-1-52. PMID: 4003988.

Digestive System Tumours WHO Classification of Tumours. (2019). *Volume 1 WHO classification of tumours editorial board*, 5e. IARC Press Lyon.

Dong, J., Maj, C., Tsavachidis, S. et al. (2013). Sex-specific genetic associations for Barrett's Esophagus and Esophageal Adenocarcinoma. *Gastroenterology* 159 (6): 2065–2076.e1. doi: 10.1053/j.gastro.2020.08.052. Epub 2020 Sep 9. PMID: 32918910.

Drovdlic, C.M., Goddard, K.A., Chak, A. et al. (2003 September). Demographic and phenotypic features of 70 families segregating Barrett's oesophagus and oesophageal adenocarcinoma. *J Med Genet* 40 (9): 651–656. DOI: 10.1136/jmg.40.9.651. PMID: 12960209; PMCID: PMC1735581.

Elster, K. (1976). Histologic classification of gastric polyps. In: *Pathology of the Gastro-intestinal Tract* (ed. B.C. Morson), 78–92. Berlin: Springer.

Eng, C., Spechler, S.J., Ruben, R., and Li, F.P. (1993 July-August). Familial Barrett esophagus and adenocarcinoma of the gastroesophageal junction. *Cancer Epidemiol Biomarkers Prev*. 2 (4): 397–399. Erratum in: (1993 September-October). *Cancer Epidemiol Biomarkers Prev* 2 (5): 505. PMID: 8348064.

Everhart, C.W., Jr, Holtzapple, P.G., and Humphries, T.J. (1983 August). Barrett's esophagus: inherited epithelium or inherited reflux? *J Clin Gastroenterol* 5 (4): 357–358. PMID: 6886360.

Fahmy, N. and King, J.F. (1993 August). Barrett's esophagus: an acquired condition with genetic predisposition. *Am J Gastroenterol* 88 (8): 1262–1265. PMID: 8338095.

Fecteau, R.E., Kong, J., Kresak, A. et al. (2016 October 1). Association between Germline mutation in VSIG10L and Familial Barrett Neoplasia. *JAMA Oncol*. 2(10):1333–1339. doi: 10.1001/jamaoncol.2016.2054. PMID: 27467440; PMCID: PMC5063702.

Fitzgerald, R.C., Hardwick, R., Huntsman, D. et al. (2010 July). International gastric cancer linkage consortium. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet* 47 (7): 436–444. doi: 10.1136/jmg.2009.074237. Erratum in: (2011 March). *J Med Genet* 48 (3): 216. Van Krieken, Nicola [corrected to Van Grieken, Nicola C]. PMID: 20591882; PMCID: PMC2991043.

Gaston, D., Hansford, S., Oliveira, C. et al. (2014 October 23). Germline mutations in MAP3K6 are associated with familial gastric cancer. *PLoS Genet* 10 (10): e1004669. doi: 10.1371/journal.pgen.1004669. PMID: 25340522; PMCID: PMC4207611.

Gayther, S.A., Gorringe, K.L., Ramus, S.J. et al. (1998 September 15). Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. *Cancer Res* 58 (18): 4086–4089.

Gharahkhani, P., Fitzgerald, R.C., Vaughan, T.L. et al. (2016 October). Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. *Lancet Oncol* 17 (10): 1363–1373. doi: 10.1016/S1470-2045(16)30240-6. Epub 2016 Aug 12. PMID: 27527254; PMCID: PMC5052458.

Global Cancer observatory. (2020). https://GECo.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf

Groves, C., Jankowski, J., Barker, F., and Holdstock, G. (2005 September). A family history of Barrett's oesophagus: another risk factor? *Scand J Gastroenterol* 40 (9): 1127–1128. doi: 10.1080/00365520510023189. PMID: 16211720.

Guilford, P., Hopkins, J., Harraway, J. et al. (1998 March 26). E-cadherin germline mutations in familial gastric cancer. *Nature* 392 (6674): 402–405. doi: 10.1038/32918. PMID: 9537325.

Hackeng, W.M., Montgomery, E.A., Giardiello, F.M. et al. (2017 March). Morphology and genetics of pyloric gland adenomas in familial adenomatous polyposis. *Histopathology* 70 (4): 549–557. doi: 10.1111/his.13105. Epub 2016 Dec 13. PMID: 27767239; PMCID: PMC5300963.

Hansford, S., Kaurah, P., Li-Chang, H. et al. (2015 April). Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol* 1 (1): 23–32. doi: 10.1001/jamaoncol.2014.168. Erratum in: (2015 April). *JAMA Oncol* 1 (1): 110. PMID: 26182300.

Helgason, H., Rafnar, T., Olafsdottir, H.S. et al. (2015 August). Loss-of-function variants in ATM confer risk of gastric cancer. *Nat Genet* 47 (8): 906–910. doi: 10.1038/ng.3342. Epub 2015 Jun 22. PMID: 26098866.

Hu, N., Wang, Z., Song, X. et al. (2016 October). Genome-wide association study of gastric adenocarcinoma in Asia: a comparison of associations between cardia and non-cardia tumours. *Gut* 65 (10):1611–1618. doi: 10.1136/gutjnl-2015-309340. Epub 2015 Jun 30. PMID: 26129866; PMCID: PMC5568652.

Huang, K.L., Mashl, R.J., Wu, Y. et al. . (2018 April 5). Pathogenic Germline variants in 10,389 adult cancers. *Cell* 173 (2): 355–370.e14. doi: 10.1016/j.cell.2018.03.039. PMID: 29625052; PMCID: PMC5949147.

Ilson, D.H., Moughan, J., Suntharalingam, M. et al. (2014). RTOG 0436: a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery [ASCO abstract 4007]. *J Clin Oncol* 32 (15). doi: 10.1200/jco.2014.32.15_suppl.4007.

Janjigian, Y.Y., Werner, D., Pauligk, C. et al. (2012 October). Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. *Ann Oncol*. 23 (10): 2656–2662. doi: 10.1093/annonc/mds104. Epub 2012 Jun 11. PMID: 22689179.

Jankowski, J.A. and Satsangi, J. (2013 April). Barrett's esophagus: evolutionary insights from genomics. *Gastroenterology* 144 (4): 667–669. doi: 10.1053/j.gastro.2013.02.014.Epub 2013 Feb 21.

Jankowski, J.A., Wright, N.A., Meltzer, S.J. et al. (1999 April). Molecular evolution of the metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. *Am J Pathol* 154 (4): 965–973. doi: 10.1016/S0002-9440(10)65346-1.

Jee, C.D., Kim, M.A., Jung, E.J. et al. (2009 May). Identification of genes epigenetically silenced by CpG methylation in human gastric carcinoma. *Eur J Cancer* 45 (7): 1282–1293. doi: 10.1016/j.ejca.2008.12.027. Epub 2009 Feb 3. PMID: 19195878.

Jin, G., Ma, H., Wu, C. et al. (2012 November 2). Genetic variants at 6p21.1 and 7p15.3 are associated with risk of multiple cancers in Han Chinese. *Am J Hum Genet*. 91(5):928–934. doi: 10.1016/j.ajhg.2012.09.009. Epub 2012 Oct 25. PMID: 23103227; PMCID: PMC3487121.

Jochem, V.J., Fuerst, P.A., and Fromkes, J.J. (1992 April). Familial Barrett's esophagus associated with adenocarcinoma. *Gastroenterology* 102 (4 Pt 1): 1400–1402. PMID: 1551547.

Jones, E.G. (1964 May). Familial Gastric Cancer. *N Z Med J* 63: 287–296. PMID: 14158754.

Kakiuchi, M., Nishizawa, T., Ueda, H. et al. (2014 June). Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. *Nat Genet* 46 (6): 583–587. doi: 10.1038/ng.2984. Epub 2014 May 11. PMID: 24816255.

Kang, G.H., Lee, S., Kim, J.S., and Jung, H.Y. (2003 April). Profile of aberrant CpG island methylation along multistep gastric carcinogenesis. *Lab Invest* 83 (4): 519–526. doi: 10.1097/01.lab.0000064704.53132.65. Erratum in: *Lab Invest* 2003 Jul;83(7):1093. PMID: 12695555.

Kim, K.M., Kwon, M.S., Hong, S.J. et al. (2003 October). Genetic classification of intestinal-type and diffuse-type gastric cancers based on chromosomal loss and microsatellite instability. *Virchows Arch* 443 (4): 491–500. doi: 10.1007/s00428-003-0840-0. Epub 2003 Aug 15. PMID: 12920592.

Kim, T.Y., Jong, H.S., Jung, Y. et al. (2004 July). DNA hypermethylation in gastric cancer. *Aliment Pharmacol Ther* 20 (Suppl 1): 131–142. doi: 10.1111/j.1365-2036.2004.01984.x. PMID: 15298619.

Krompecher, E. (1924). Basalzellen, Metaplasie und Regeneration. *Beitr path Anat* 72: 163–183. (2004). Pneumologie 58 (9): 680–685. DOI: 10.1055/ s-2004-818417.

Kushima, R., Sekine, S., Matsubara, A. et al. (2013 June). Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. *Pathol Int* 63 (6): 318–325. doi: 10.1111/pin.12070. PMID: 23782334.

Kwon, C.H., Kim, Y.K., Lee, S. et al. (2018 March). Gastric poorly cohesive carcinoma: a correlative study of mutational signatures and prognostic significance based on histopathological subtypes. *Histopathology* 72 (4): 556–568. doi: 10.1111/his.13383. Epub 2017 Nov 29. PMID: 28873240.

Le, D.T., Uram, J.N., Wang, H. et al. (2015 June 25). PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 372 (26): 2509–2520. doi: 10.1056/NEJMoa1500596. Epub 2015 May 30. PMID: 26028255; PMCID: PMC4481136.

Lennerz, J.K., Kwak, E.L., Ackerman, A. et al. (2011). MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. *J Clin Oncol* 29 (36): 4803–4810. doi: 10.1200/JCO.2011.35.4928. Epub 2011 Oct 31. PMID: 22042947; PMCID: PMC3255989.

Lichtenstein, P., Holm, N.V., Verkasalo, P.K. et al. (2000 July 13) Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343 (2): 78–85. doi: 10.1056/NEJM200007133430201. PMID: 10891514.

Lott, P.C. and Carvajal-Carmona, L.G. (2018 December). Resolving gastric cancer aetiology: an update in genetic predisposition. *Lancet Gastroenterol Hepatol* 3 (12): 874–883. doi: 10.1016/S2468-1253(18)30237-1. PMID: 30507471; PMCID: PMC6500447.

Majewski, I.J., Kluijt, I., Cats, A. et al. (2013 March). An α-E-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer. *J Pathol*. 229 (4): 621–629. doi: 10.1002/path.4152. PMID: 23208944.

Melzer, E., Shtoyerman, R., Appelman, Z., and Kashtan, H. (2006 March). Familial Barrett's adenocarcinoma. *Am J Gastroenterol* 101 (3):677. doi: 10.1111/j.1572-0241.2006.473_7.x. PMID: 16542304.

Mikhail, S., Ciombor, K., Noonan, A. et al. (2015 September 8). Upfront molecular testing in patients with advanced gastro-esophageal cancer: is it time yet? *Oncotarget* 6 (26): 22206–22213. doi: 10.18632/oncotarget.4247. PMID: 26082439; PMCID: PMC4673157.

Müller-Höcker, J. and Rellecke, P. (2003 May). Chief cell proliferation of the gastric mucosa mimicking early gastric cancer: an unusual variant of fundic gland polyp. *Virchows Arch*. 442 (5): 496–500. doi: 10.1007/s00428-003-0780-8. Epub 2003 Apr 16. PMID: 12698365.

Munitiz, V., Parrilla, P., Ortiz, A. et al. (2008 August). High risk of malignancy in familial Barrett's esophagus: presentation of one family. *J Clin Gastroenterol*. 42 (7): 806–809. doi: 10.1097/MCG.0b013e3180329015. PMID: 18385604.

Muro, K., Chung, H.C., Shankaran, V. et al.(2016 June) Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 2016 Jun;17(6):717–726. doi: 10.1016/S1470-2045(16)00175-3. PMID: 27157491.

Oliveira, C., Pinheiro, H., Figueiredo, J. et al. (2015 February). Familial gastric cancer: genetic susceptibility, pathology, and implications for management. *Lancet Oncol* 16 (2): e60–70. doi: 10.1016/S1470-2045(14)71016-2. PMID: 25638682.

Oliveira, C., Seruca, R., Hoogerbrugge, N. et al. (2013 August). Clinical utility gene card for: hereditary diffuse gastric cancer (HDGC). *Eur J Hum Genet* 21 (8). doi: 10.1038/ejhg.2012.247. Epub 2013 Feb 27. PMID: 23443028; PMCID: PMC3722670.

Park, C., Cho, J., Lee, J. et al. (2017 August 10). Host immune response index in gastric cancer identified by comprehensive analyses of tumor immunity. *Oncoimmunology* 6 (11): e1356150. doi: 10.1080/2162402X.2017.1356150. PMID: 29147610; PMCID: PMC5674954.

Pharoah, P.D., Guilford, P., and Caldas, C. (2001 December). International gastric cancer linkage consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology* 121 (6): 1348–1353. doi: 10.1053/gast.2001.29611. PMID: 11729114.

Poynton, A.R., Walsh, T.N., O'Sullivan, G., and Hennessy, T.P. (1996 September). Carcinoma arising in familial Barrett's esophagus. *Am J Gastroenterol* 91 (9): 1855–1856. PMID: 8792715.

Ratti, M., Lampis, A., Hahne, J.C. et al. (2018 November). Microsatellite instability in gastric cancer: molecular bases, clinical perspectives, and new treatment approaches. *Cell Mol Life Sci* 75 (22): 4151–4162. doi: 10.1007/s00018-018-2906-9. Epub 2018 Sep 1. PMID: 30173350; PMCID: PMC6182336.

Refolo, M.G., Lotesoriere, C., Messa, C. et al. (2020 August). Integrated immune gene expression signature and molecular classification in gastric cancer: new insights. *J Leukoc Biol* 108 (2): 633–646. doi: 10.1002/JLB.4MR0120-221R. Epub 2020 Mar 14. PMID: 32170872.

Reid, B.J., Li, X., Galipeau, P.C., and Vaughan, T.L. (2010 February). Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis. *Nat Rev Cancer* 10 (2): 87–101. doi: 10.1038/nrc2773. PMID: 20094044; PMCID: PMC2879265.

Rentien, A.L., Lévy, M., Copie-Bergman, C. et al. (2018 February). Long-term course of precancerous lesions arising in patients with gastric MALT lymphoma. *Dig Liver Dis* 50 (2): 181–188. doi: 10.1016/j.dld.2017.10.014. Epub 2017 Oct 27. PMID: 29102522.

Rodriquenz, M.G., Roviello, G., D'Angelo, A. et al. (2020 May 11). MSI and EBV positive gastric cancer's subgroups and their link with novel immunotherapy. *J Clin Med* 9 (5): 1427. doi: 10.3390/jcm9051427. PMID: 32403403; PMCID: PMC7291039.

Study Group of Millennium Genome Project for Cancer Sakamoto, H., Yoshimura, K., Saeki, N. et al. (2008 June). Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. *Nat Genet* 40 (6): 730–740. doi: 10.1038/ng.152. Epub 2008 May 18. PMID: 18488030.

Sakurai, U., Lauwers, G.Y., Vieth, M. et al. (2014 November). Gastric high-grade dysplasia can be associated with submucosal invasion: evaluation of its prevalence in a series of 121 endoscopically resected specimens. *Am J Surg Pathol* 38 (11): 1545–1550. doi: 10.1097/PAS.0000000000000274. PMID: 25310837.

Sappati Biyyani, R.S., Chessler, L., McCain, E. et al. (2007). Familial trends of inheritance in gastro esophageal reflux disease, Barrett's esophagus and Barrett's adenocarcinoma: 20 families. *Dis Esophagus* 20 (1): 53–57. doi: 10.1111/j.1442-2050.2007.00651.x. PMID: 17227311.

Schlemper, R.J., Itabashi, M., Kato, Y. et al. (1997 June 14) Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. *Lancet* 349 (9067): 1725–1729. doi: 10.1016/S0140-6736(96)12249-2. Erratum in: Lancet 1997 Aug 16;350(9076):524. PMID: 9193382.

Schlemper, R.J., Kato, Y., and Stolte, M. (2001 July). Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. *J Gastroenterol* 36 (7): 445–456. doi: 10.1007/s005350170067. PMID: 11480788.

Shah, M.A., Khanin, R., Tang, L. et al. (2011 May 1). Molecular classification of gastric cancer: a new paradigm. *Clin Cancer Res* 17 (9): 2693–2701. doi: 10.1158/1078-0432.CCR-10-2203. Epub 2011 Mar 23. PMID: 21430069; PMCID: PMC3100216.

Shen, L., Li, J., Xu, J. et al. (2015 January). Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 18 (1): 168–176. doi: 10.1007/s10120-014-0351-5. Epub 2014 Feb 21. PMID: 24557418; PMCID: PMC4544634.

Shi, L., Zhao, M., Luo, Q. et al. (2010 June) Overexpression of PIP5KL1 suppresses cell proliferation and migration in human gastric cancer cells. *Mol Biol Rep* 37 (5): 2189–2198. doi: 10.1007/s11033-009-9701-5. Epub 2009 Aug 13. PMID: 19680787.

Shi, Y., Hu, Z., Wu, C. et al. (2011 October 30). A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. *Nat Genet* 43 (12): 1215–1218. doi: 10.1038/ng.978. PMID: 22037551.

Shibuya, M. (2011 December). Vascular Endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies. *Genes Cancer*. 2(12):1097–1105. doi: 10.1177/1947601911423031. PMID: 22866201; PMCID: PMC3411125.

Shimura, T., Toden, S., Kandimalla, R. et al. (2021 November 1). Genomewide expression profiling identifies a novel miRNA-based signature for the detection of peritoneal metastasis in patients with gastric cancer. *Ann Surg* 274 (5): e425–e434. doi: 10.1097/SLA.0000000000003647. PMID: 31663973; PMCID: PMC7577555.

Su, Z., Gay, L.J., Strange, A. et al. (2012 October). Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. *Nat Genet* 44 (10): 1131–1136. doi: 10.1038/ng.2408. Epub 2012 Sep 9.

Syngal, S., Brand, R.E., Church, J.M. et al. (2015 February). American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 110 (2): 223–262. quiz 263. doi: 10.1038/ajg.2014.435. Epub 2015 Feb 3. PMID: 25645574; PMCID: PMC4695986.

Takahashi, T. and Iwama, N. (1985). Three-dimensional microstructure of gastrointestinal tumors. Gland pattern and its diagnostic significance. *Pathol Annu* 20 Pt 1: 419–440. PMID: 3887299.

Tan, I.B., Ivanova, T., Lim, K.H. et al. (2011 August). Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology*. 141 (2): 476–85, 485.e1–11. doi: 10.1053/j.gastro.2011.04.042. Epub 2011 Apr 28. PMID: 21684283; PMCID: PMC3152688.

Taylor, P.R., Abnet, C.C., and Dawsey, S.M. (2013 April). Squamous dysplasia–the precursor lesion for esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 22 (4): 540–552. doi: 10.1158/1055-9965.EPI-12-1347. PMID: 23549398; PMCID: PMC3681095.

Tew, W.P., Kelsen, D.P., and Ilson, D.H. (2005 September). Targeted therapies for esophageal cancer. *Oncologist* 10 (8): 590–601. doi: 10.1634/theoncologist.10-8-590. PMID: 16177283.

To, H., Clemons, N.J., Duong, C.P. et al. (2016 July). The genetics of Barrett's Esophagus: a Familial and Population-Based Perspective. *Dig Dis Sci* 61 (7): 1826–1834. doi: 10.1007/s10620-016-4109-2. Epub 2016 Mar 12. PMID: 26971090.

To, K.F., Leung, W.K., Lee, T.L. et al. (2002 December 20). *Promoter hypermethylation of tumor-related genes in gastric intestinal metaplasia of patients with and without gastric cancer*. Int J Cancer. 2002 Dec 20;102(6):623-8. doi: 10.1002/ijc.10783. PMID: 12448005.

Ueda, T., Volinia, S., Okumura, H. et al. (2010 February). Relation between micro RNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncl* 11 (2): 136–146; PMID: 20022810.

Ushiku, T., Kunita, A., Kuroda, R. et al. (2020 February). Oxyntic gland neoplasm of the stomach: expanding the spectrum and proposal of terminology. *Mod Pathol* 33(2):206–216. doi: 10.1038/s41379-019-0338-1. Epub 2019 Aug 2. PMID: 31375767.

van Nistelrooij, A.M.J., van Marion, R., van Ijcken, W.F.J. et al. (2018 July). Germline variant in MSX1 identified in a Dutch family with clustering of Barrett's esophagus and esophageal adenocarcinoma. *Fam Cancer* 17 (3): 435–440. doi: 10.1007/s10689-017-0054-2. PMID: 29134539; PMCID: PMC5999157.

Vieth, M., Kushima, R., Borchard, F., and Stolte, M. (2003 April) Pyloric gland adenoma: a clinico-pathological analysis of 90 cases. *Virchows Arch* 442 (4): 317–321. doi: 10.1007/s00428-002-0750-6. Epub 2003 Mar 26. PMID: 12715167.

Vieth, M., Montgomery, E.A., and Riddell, R.H. (2016). Observations of different patterns of dysplasia in barretts esophagus - a first step to harmonize grading. *Cesk Patol* 52 (3): 154–163. English. PMID: 27526016.

Vieth, M. and Stolte, M. (2005). Distinction of High-Grade Intraepithelial Neoplasia and Tubular Gastric Adenocarcinoma. In: *The Diversity of Gastric Carcinoma* (ed. M. Kaminishi, K. Takubo, and K. Mafune). Tokyo: Springer. doi: 10.1007/4-431-27713-7_7.

Vieth, M. and Stolte, M. (2005 December). Pathology of early upper GI cancers. *Best Pract Res Clin Gastroenterol*. 19 (6): 857–869. doi: 10.1016/j.bpg.2005.02.008 PMID: 16338646.

Wanebo, H.J., Kennedy, B.J., Chmiel, J. et al. (1993 November). Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg*. 218 (5): 583–592. doi: 10.1097/00000658-199321850-00002. PMID: 8239772; PMCID: PMC1243028.

Wang, C., Wang, L., Liang, B. et al. (2021 May). Synergistic antitumor effect of the anti-ErbB2 antibodies trastuzumab and H2-18 on trastuzumab-resistant gastric cancer cells. *Oncol Lett* 21 (5): 400. doi: 10.3892/ol.2021.12661. Epub 2021 Mar 18. PMID: 33777223; PMCID: PMC7988693.

Wang, K., Yuen, S.T., Xu, J. et al. (2014 June). Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* 46 (6): 573–582. doi: 10.1038/ng.2983. Epub 2014 May 11. PMID: 24816253.

Wang, Z., Dai, J., Hu, N. et al. (2017 April). Identification of new susceptibility loci for gastric non-cardia adenocarcinoma: pooled results from two Chinese genome-wide association studies. *Gut* 66 (4): 581–587. doi: 10.1136/gutjnl-2015-310612. Epub 2015 Dec 23. PMID: 26701879; PMCID: PMC4963301.

Wei, B., Tai, Y., Tong, H. et al. (2017 August 1). Correlations between VEGF-A expression and prognosis in patients with gastric adenocarcinoma. *Int J Clin Exp Pathol* 10 (8): 8461–8469. PMID: 31966698; PMCID: PMC6965380.

Westerterp, M., Koppert, L.B., Buskens, C.J. et al. (2005 May). Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastroesophageal junction. *Virchows Arch* 446 (5): 497–504. doi: 10.1007/s00428-005-1243-1. Epub 2005 Apr 19. PMID: 15838647.

Wilke, H., Van Cutsem, E., Oh, S.C. et al. (2014). RAINBOW: a global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy: results of a multiple Cox regression analysis adjusting for prognostic factors. *J Clin Oncol* 32 (15): 10.1200.

Wong, S.S., Kim, K.M., Ting, J.C. et al. (2014 November 19 Genomic landscape and genetic heterogeneity in gastric adenocarcinoma revealed by whole-genome sequencing. *Nat Commun* 5: 5477. doi: 10.1038/ncomms6477 PMID: 25407104.

Wu, M.S., Chang, M.C., Huang, S.P. et al. (2001 January). Correlation of histologic subtypes and replication error phenotype with comparative genomic hybridization in gastric cancer. *Genes Chromosom Cancer* 30 (1): 80–86. doi: 10.1002/1098-2264(2000)9999:9999<::aid-gcc1062>3.0.co;2-r. PMID: 11107179.

Yan, C., Zhu, M., Ding, Y. et al. (2020 April). Meta-analysis of genome-wide association studies and functional assays decipher susceptibility genes for gastric cancer in Chinese populations. *Gut* 69 (4): 641–651. doi: 10.1136/gutjnl-2019-318760. Epub 2019 Aug 5. PMID: 31383772.

Yao X, Ajani JA, Song S. Molecular biology and immunology of gastric cancer peritoneal metastasis. Transl Gastroenterol Hepatol. 2020 Oct 5;5:57. doi: 10.21037/tgh.2020.02.08. PMID: 33073052; PMCID: PMC7530317.

Yoon, H.H., Bendell, J.C., Braiteh, F.S. et al. (2016 December). Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. *Ann Oncol* 27 (12): 2196–2203. doi: 10.1093/annonc/mdw423. Epub 2016 Oct 20. Erratum in: Ann Oncol. 2019 Dec 1;30(12):2016. PMID: 27765757; PMCID: PMC7360144.

Zanghieri, G., Di Gregorio, C., Sacchetti, C. et al. (1990 November 1). Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. *Cancer* 66 (9): 2047–2051. doi: 10.1002/1097-0142(19901101)66:9<2047::aid-cncr2820660934>3.0.co;2-g. PMID: 2224804.Format.

Zhang, T., Zhang, L., Fan, S. et al. (2015 July 28). Patient-derived gastric carcinoma xenograft mouse models faithfully represent human tumor molecular diversity. *PLoS One* 10 (7): e0134493. doi: 10.1371/journal.pone.0134493. PMID: 26217940; PMCID: PMC4517891).

3 Screening, Surveillance, and Prevention of Esophageal and Gastric Cancers

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[Aspects of relevant colorectal data are covered in Chapter 11].

Introduction

Upper gastrointestinal (GI) cancers remain among the most important cancers worldwide. In 2020, gastric cancer ranked fifth (1,089,103 new cases, 5.6%) in terms of incidence and fourth (768,793 deaths, 7.7%) in terms of mortality globally (Sung et al. 2021). However, in South Central Asian countries such as Iran, Afghanistan, and Turkmenistan, it is the leading cause of cancer-related deaths. Esophageal cancer ranks seventh in terms of incidence (604,100 new cases, 3.1%) and sixth in terms of mortality (544,076 deaths, 5.5%) (Sung et al. 2021). The incidence of esophageal cancer varies according to histologic subtypes and geography. The highest incidence rates of esophageal adenocarcinoma (EAC) are in the Netherlands (age-standardized rate (ASR): 7.7) and the United Kingdom (ASR: 7.5), while Malawi (ASR: 21), Mongolia (ASR: 20.9), Kenya (ASR: 20.3), and China (ASR: 18.8) are among the countries with the highest incidence of esophageal squamous cell carcinoma (ESCC) (Huang et al. 2021).

The prognosis of upper GI cancers is generally poor, mainly due to their late diagnosis. For example, the overall five-year survival rate for patients with esophageal cancer is below 20%, although the rate can be improved to nearly 50% with neoadjuvant chemoradiotherapy and surgery (Huang et al. 2021; Shapiro et al. 2015). Similarly, the survival rate among patients with gastric cancer is less than 10% when the cancer is diagnosed at an advanced stage but is significantly improved, by up to 85%, if it is detected early (Wang et al. 2004). Due to the aggressive nature of these cancers, it is critical to detect the precursor lesions/early cancers. In the long run, the aim is to reduce the disease burden, reverse the incidence trend, and eventually improve the patients' outcomes. In this chapter, the risk factors, screening, and surveillance strategies, and preventive measures for upper GI cancers – namely, esophageal and gastric cancers – will be discussed.

Esophageal Cancer

Risk Factors for Esophageal Adenocarcinoma

Non-modifiable Risk Factors

The incidence of EAC increases with age, especially after the age of 50 years, with a significant male predilection (6- to 8-fold higher risk than females) (Bhat et al. 2011). Compared to ESCC, EAC is more prevalent in the West. Data from the cancer registry in the United States (Surveillance, Epidemiology, and End Results (SEER)) demonstrated a five-times higher incidence rate of EAC among whites compared to that among blacks. Compared with Hispanics, whites had a 200% increased risk of EAC (Cook et al. 2009). Although there is no recognized familial syndrome related to EAC, some studies that evaluated the role of germline mutation in EAC development have found a few susceptible genetic loci, such as TBX1, FOXP1, FOXF1, BARX1, HLA, and CRTC1 (Levine et al. 2013; Su et al. 2012). However, the use of genetics in clinical practice to predict the risk of EAC is still limited and it does not offer greater sensitivity when used in combination with other EAC risk factors (Dong et al. 2018) (see Table 1).

Modifiable Risk Factors

Obesity has become a global pandemic and is associated with a higher risk of getting major non-communicable diseases, including type 2 diabetes, coronary heart disease, stroke, and cancers. A recent meta-analysis that included more than 280 population-based studies worldwide has estimated a global prevalence of central obesity in adults to be 41.5%; it was 31.3% in the 1990s (Wong et al. 2020). Obesity has been linked to the development of EAC via, for example, a higher prevalence of gastroesophageal

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Table 1 Non-modifiable and modifiable risk factors.

Types of cancers	Risk factors	
	Non-modifiable	**Modifiable**
Esophageal adenocarcinoma	Age > 50 years Male sex White race Family history Germline mutation: TBX1, FOXP1, FOXF1, BARX1, HLA, CRTC1	Chronic GERD symptoms Cigarette smoking Processed meat intake
Esophageal squamous cell carcinoma	Male sex (in low-prevalence area such as the United State male-to-female ratio = 4:1) Germline mutation: PLCE1, TP53, HLA II, CDKN2A, cyclin D1, CDK4/6, RB1, NFE2L2, CHEK1, CHEK2, NOTCH1, NOTCH3 Associated Diseases: Tylosis Achalasia Head and neck squamous cell carcinoma	Cigarette smoking Alcohol consumption Pickled vegetables High-temperature drinks
Gastric cancer	Age > 50 years Male sex (5-fold for cardia, 2-fold for non-cardia) Family history East Asian countries Hereditary syndromes: HDGC Peutz-Jeghers syndrome Juvenile polyposis Lynch syndrome Hereditary breast/ovarian cancer syndrome Familial adenomatous polyposis	*Helicobacter pylori* infection Cigarette smoking Obesity (cardia type) Moderate-high salt intake Pickled/smoked/dried foods Western/unhealthy diet Red/processed meat intake

GERD, gastroesophageal reflux disease; HDGC, hereditary diffuse gastric cancer.

reflux disease (GERD), higher incidence of Barrett's esophagus (BE), the role of systemic inflammation and adipokines, alteration of esophageal microbiota due to high-fat diets, and the effect of insulin resistance (Schlottmann et al. 2020).

GERD is a well-documented risk factor for EAC. A landmark Swedish-population-based case-control study in 1999 demonstrated an odds ratio (OR) of 7.7 for EAC in individuals with recurrent reflux symptoms. The likelihood of EAC was much higher in those with long-standing and severe reflux symptoms (OR: 43.5), and this risk was not associated with ESCC (OR: 1.1) (Lagergren et al. 1999). Obese individuals are more likely to experience GERD symptoms. In a cross-sectional study involving 453 volunteers, a dose–response relationship between the frequency of GERD symptoms and a higher body mass index (BMI) was found, whereby 35% of symptomatic individuals were overweight (BMI 25–30) and 39% were obese (BMI > 30) (El-Serag et al. 2005). Many studies have also shown a positive association between obesity, central adiposity, and a higher waist-to-hip ratio with BE (Baik et al. 2017; Edelstein et al. 2007; Stein et al. 2005). In addition, the mean BMI was found to be higher in patients with long-segment BE as compared to those with short-segment BE (32.7 vs. 30.3, $P = 0.001$) (Abdallah et al. 2015). The higher prevalence of BE in obesity is most likely due to the co-existing GERD, although this association may not be related to the presence of GERD, as shown by a meta-analysis of 17 studies (adjusted OR: 1.98) (Singh et al. 2013a).

Apart from the reflux phenomenon, systemic inflammation and adipokines (e.g., adiponectin and leptin) have also been implicated in EAC in obese individuals. Adiponectin regulates cell proliferation, induces apoptosis, inhibits growth factors, and has anti-inflammatory effects (Barb et al. 2007). The plasma level of adiponectin has been shown to be inversely associated with other cancers, such as breast, endometrial, and colorectal cancers (Dal Maso et al. 2004; Tworoger et al. 2007; Wei et al. 2005). Specific to esophageal adenocarcinoma, a high level of adiponectin was associated with a less advanced tumor stage (Howard et al. 2014) and a lower risk of BE progression to adenocarcinoma (Duggan et al. 2013). Leptin, however, was shown to be positively associated with BE (adjusted OR: 3.25) (Rubenstein et al. 2013).

A high plasma level of leptin might activate the production of inflammatory cytokines, such as TNF-alpha, IL-2, and IL-6, which might contribute to the development of dysplastic BE and the progression of tumor (Dvorak et al. 2007; Fernadez-Riejos et al. 2010; Tselepis et al. 2002).

Cigarette smoking is moderately associated with the development of EAC. A pooled analysis from 10 population-based case-control studies and two cohort studies demonstrated an OR of 1.96 and 2.18 for EAC and esophagogastric junctional adenocarcinoma, respectively. Furthermore, there was a strong dose–response association between pack years of cigarette smoking and EAC ($p < 0.001$) (Cook et al. 2010). This association has been confirmed by a recent meta-analysis, with a relative risk of 1.66 in former smokers and 2.34 in current smokers (Wang et al. 2017). Unlike ESCC, alcohol consumption is not associated with EAC (Anderson et al. 2009).

Though diet has been proposed as a possible risk factor for EAC, the evidence is inconclusive. A large prospective cohort study did not show a significant inverse association between total fruit and vegetable intake and EAC risk (hazard ratio (HR): 0.98), except for spinach intake (Freedman et al. 2007). On the contrary, processed meat intake was associated with an increased risk of EAC (Salehi et al. 2013).

Risk Factors for Esophageal Squamous Cell Carcinoma

Non-modifiable Risk Factors

The gender predilection for ESCC depends on geographical areas. The male-to-female ratio is approximately 4:1 in the United States and nearly 1:1 in China and Iran (Abnet et al. 2018). It is most prevalent in central Asia, spanning China, northern Iran, and Turkey (esophageal cancer belt).

Genetic factors might play a role in ESCC development, as shown in a population-based case-control study in Taixing, China. It demonstrated an almost doubled risk of ESCC in individuals with a positive family history of esophageal cancer among first-degree relatives (OR: 1.85). The ESCC risk was further increased by eight-fold if both parents had esophageal cancer (Chen et al. 2015). Although no specific gene mutation has been strongly attributed to ESCC, several studies did identify germline mutation in PLCE1, TP53, HLA class II, CDKN2A, cyclin D1, CDK4/6, RB1, NFE2L2, CHEK1, CHEK2, NOTCH1, and NOTCH3 (Abnet et al. 2010; Cheng et al. 2016; Gao et al. 2014; Wang et al. 2010). Although none of these are currently being applied clinically, the research area in genomic study is expanding, especially since the emergence of genome-wide association study (GWAS).

Tylosis (Howel–Evans syndrome) and to some extent achalasia have a strong link with ESCC. Tylosis is a rare autosomal dominant disease characterized by hyperkeratosis of the palms and soles, and there is a 90% risk of ESCC in late-onset tylosis (Marger and Marger 1993). Achalasia carries up to 50-fold increased risk of ESCC, especially after 10 years of the initial diagnosis (Leeuwenburgh et al. 2010; Meijssen et al. 1992). Patients with head and neck squamous cell carcinoma (HNSCC) also have an increased risk of ESCC. A population-based cohort study showed that among patients with HNSCC, the excess risk of second cancer, calculated by using the standardized incidence ratio, was 21.8 for esophageal cancer (Jain et al. 2013). Other prospective studies have shown a prevalence of synchronous or metachronous ESCC of 3.8% to 14.9% (Chaber-Ciopinska et al. 2016).

Modifiable Risk Factors

A strong association between cigarette smoking and alcohol consumption has been linked to the development of ESCC, with a three- to five-fold increased risk of ESCC in current smokers as compared to non-smokers (Wang et al. 2017). Additionally, studies around the globe have observed a six- to nine-fold increased risk of ESCC with excess alcohol intake (Garidou et al. 1996; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012; Lagergren et al. 2000; Pan et al. 2017). Furthermore, both these lifestyle factors seem to have a synergistic effect in further increasing the ESCC risk up to 12-fold and 19-fold in men and women, respectively (Castellsague et al. 1999).

Regarding the role of diet in ESCC, a potential causal relationship has been found with consuming pickled vegetables (OR: 2.08) (Islami et al. 2009b) and drinking high-temperature beverages (Islami et al. 2009a), while a higher intake of fruits and vegetables seems to have protective effect (Engel et al. 2003; Howard et al. 2014).

Precursor Lesion: Barrett's Esophagus

BE is a precursor lesion for EAC in the metaplasia–dysplasia–adenocarcinoma sequence, with a prevalence of approximately 0.8% in the general population and 3% in those with GERD (Qumseya et al. 2019). The diagnosis of BE requires the endoscopic appearance of metaplastic columnar epithelium (described as salmon-pink color) above the gastroesophageal junction, replacing the normal distal squamous epithelial lining (see Figure 1), together with histopathological confirmation (intestinal metaplasia with or without goblet cells) from esophageal biopsies (Fitzgerald et al. 2014). On the basis of the maximal length endoscopically, BE can be divided into short (<3cm) and long segments (≥3cm).

BE is more prevalent in males and typically diagnosed after their sixth decade of life. In a retrospective cross-sectional study involving 155,641 patients undergoing upper gastrointestinal endoscopy, the BE yield increased steeply from the third decade of life (2.1%) to the sixth decade (9.3%) and then plateaued thereafter (Rubenstein et al. 2010a). Other significant risk factors for BE are white race, chronic GERD, central obesity, cigarette smoking, and a family history of BE/EAC (Sanghi and Thota 2019).

The risk of EAC in BE increases with increasing BE length and grade of dysplasia. In a study involving 1017 patients, the annual cancer transition rates for patients with long (≥3 cm), short (<3

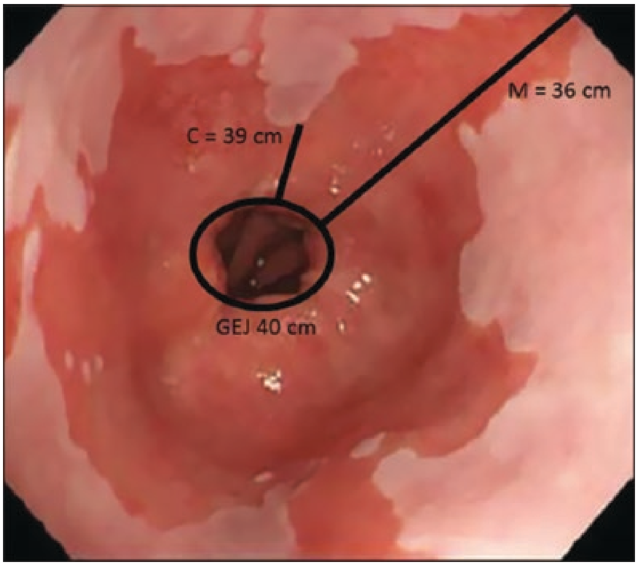

Figure 1 Endoscopic view of salmon-pink coloured of columnar lined esophagus, consistent with Barrett's esophagus. The Prague classification is C1, M4 (Schoofs et al. 2017/Hellenic Society of Gastroenterology).

cm), and ultra-short (<1 cm) BE were 0.22%, 0.03%, and 0.01%, respectively (Pohl et al. 2016). A recent meta-analysis of 2694 patients demonstrated an annual progression rate of BE to adenocarcinoma of 0.54% (Singh et al. 2014b). Concerning the grade of dysplasia, the annual risk of EAC with non-dysplastic BE is 0.33%, increasing to 0.54% for low-grade dysplasia and steeply rising to 7% for high-grade dysplasia (Shaheen et al. 2016). A meta-analysis in 2017 concluded that the risk of progression to high-grade dysplasia or EAC was higher with the presence of low-grade dysplasia in BE (OR: 4.2) (Krishnamoorthi et al. 2018).

Screening

Screening for Barrett's Esophagus

Patients with esophageal cancer usually present late due to the lack of symptoms during the early stages of cancer. Screening aims to detect the precursor lesions and subsequently offers close surveillance or early eradication treatment. In a prospective Dutch cohort study, EAC was detected at a significantly earlier stage during endoscopic surveillance for BE as compared to the general population (92% vs. 15%). This study has also shown a greater five-year survival benefit in the surveillance group as compared to the general population, that is, 74% vs. 15%, respectively (Kastelein et al. 2016).

However, population-based or mass endoscopic screening is not deemed to be efficient or cost effective and is not recommended by major gastrointestinal societies in the United States, the United Kingdom, and Europe (Li et al. 2019). Nevertheless, these societies do advocate screening for BE in high-risk individuals. The American College of Gastroenterology (ACG) and the British Society of Gastroenterology (BSG) recommend BE screening for patients with chronic (>5 years) and/or frequent (≥weekly) GERD symptoms who have three or more of the following risk factors: being male, being 50 years old or older, being Caucasian, being a tobacco smoker, being obese, and having first-degree relatives with a family history of BE or EAC (Shaheen et al. 2016). BSG further recommends lowering the threshold of these multiple risk factors in the presence of that family history (Fitzgerald et al. 2013). Although the Asia Pacific consensus has acknowledged the above recommendation from the West, the experts did not suggest BE screening based on prolonged GERD symptoms. This is due to low disease prevalence and burden in the Asia Pacific region. Furthermore, the majority of symptomatic patients will usually be subjected to diagnostic oesophagogastroduodenoscopy (OGD) anyway to exclude peptic ulcer disease or malignancy (Fock et al. 2016).

For individuals subjected to BE screening, one-time OGD is the gold standard procedure, together with four-quadrant biopsies at the suspected BE site for every 1–2 cm as per Seattle protocol (Levine et al. 1993). In the case of moderate-to-severe esophagitis, repeat endoscopy is warranted (usually by 2–3 months) after proton pump inhibitor therapy to ensure resolution and subsequently perform the biopsy protocol as indicated (Shaheen et al. 2016). One limitation of BE screening is the lack of typical GERD symptoms in nearly 50% of the patients diagnosed with EAC (Rubenstein et al. 2010b). Additionally, a systematic review demonstrated that only 4.7% of EAC patients who underwent resection had been previously diagnosed with BE (Dulai et al. 2002). Therefore, the current screening strategy that mainly targets individuals with GERD symptoms might have a limited impact on reducing the incidence of EAC and the mortality rate (Mansour et al. 2017).

Other Screening Methods for Barrett's Esophagus – Currently Unproven for Clinical Use

Another potential limitation of screening is the application of OGD as a screening tool. Although generally safe, OGD is associated with small risk of complications such as sedation risk, aspiration, bleeding, perforation, and discomfort during/after the procedure. The associated cost is another limiting factor. Alternative screening tools have been explored, including unsedated transnasal endoscopy (uTNE), cytology retrieval devices, esophageal capsule endoscopy, and biomarkers. uTNE can be performed with topical anesthesia without sedation. This greatly improves patients' comfort, safety, and willingness to undergo BE screening (Jobe et al. 2006; Peery et al. 2012, 2012; Shariff et al. 2012; Thota et al. 2005). When comparing with gold standard OGD, uTNE had excellent sensitivity (98%) and specificity (91%) for detecting the columnar lined esophagus for intestinal metaplasia (IM), with 100% specificity (Peery et al. 2012). It is also much cheaper than sedated OGD, as shown in a randomized controlled trial, with a mean cost difference of USD 1386.72

(Moriarty et al. 2018). These advantages encourage the use of uTNE as a BE screening tool at the hospital, at the bedside office, or in mobile community settings.

One of the non-invasive methods of BE screening that use a cytology sampling device is a cytosponge. It is a mesh surrounded by a gelatin capsule attached to a string and passed transorally (Ross-Innes et al. 2015). The capsule dissolves five minutes post-ingestion and expands the mesh to a sphere of 3 cm. The collected distal esophageal samples is then stained with Trefoil Factor 3 (TFF3), a biomarker for specialized IM (Maitra et al. 2020). A cytosponge with TFF3 had a sensitivity of 73.3% and a specificity of 93.8% for detecting BE (Kadri et al. 2010). When compared with screening OGD, a cytosponge can reduce the cost by 27–29% (Heberle et al. 2017). In addition to TFF3, other biomarkers for BE can be applied to improve the sensitivity, such as TFPI2, TWIST1, ZNF345, and ZNF569 (Chettouh et al. 2018; Pohl et al. 2016). However, two of the larger trials (BEST 1 and 2) excluded short segment noncircumferential BE, which is considered important in the USA (Chandar et al. 2020). Furthermore, the analysis of immunohistochemistry on cytology which is qualitative and requires considerable expertise, not widely available. To circumvent these problems competitor devices such as EsophaCap (another sponge on the string device but smaller), uses methylated DNA biomarkers to provide greater quantifiable (and perhaps less subjective) information (Chandar et al. 2020). EsoCheck uses a different swallowable encapsulated balloon which only deploys in the high-risk lower esophageal sphincter area and then the balloon inverts back into the capsule sheath before withdrawal to minimize contamination with more proximal cells as in contemporary sponge methods (Chandar et al. 2020).

New different technologies have been invented and evaluated in pilot studies, with promising sensitivity, such as esophageal capsule endoscopy (EsohaCap) and balloon cytology (Falk et al. 1997; Iyer et al. 2018; Moinova et al. 2018). Esophageal capsule endoscopy is a non-invasive, unsedated imaging technique that allows the visualization of the esophageal mucosa. From a meta-analysis with pooled participants of 618 patients, capsule endoscopy showed a moderate sensitivity of 77% and specificity of 86% (Bhardwaj et al. 2009). It is safe and easy to conduct, and currently various sample collection designs and lower cost versions are being trialed.

The screening method involving the use of blood samples for detecting circulating microRNAs (miRNAs) has been explored recently. miRNAs are endogenous, small non-coding RNAs that regulate cell growth, differentiation, proliferation, apoptosis, and metabolism and perform as post-transcriptional regulators of gene expression (Aalami et al. 2021). These miRNAs are dysregulated and altered, and their presence in the blood could serve as a biomarker for BE and early AEC. A pilot study of 41 patients with BE and 15 controls that used a panel of four circulating miRNAs (miRNA-95-3p, -136-5p, -194-5p, and -451a) revealed a sensitivity and specificity of 78% and 86%, respectively (Bus et al. 2016). Another circulating miRNA that has been studied is miR-21. It has the highest pooled sensitivity and specificity (72% and 82%, respectively) for gastrointestinal cancers, such as colorectal cancer, gastric cancer, hepatocellular carcinoma, and esophageal cancer (Chettouh et al. 2018). However, it cannot discriminate between subgroups of gastrointestinal cancers and, therefore, is not useful as a screening biomarker. Nevertheless, it might play a role in monitoring disease progression or treatment response.

Screening for Esophageal Squamous Cell Carcinoma

Unlike EAC, there are no established guidelines to screen for ESCC, either in the West or in the East, due to variable incidence rates and limited evidence to support mortality benefits or cost-effectiveness (Li et al. 2019). Nonetheless, a few studies have been conducted in high-incidence regions (≥30 cases per 100,000 persons per year) in China to evaluate the efficacy of ESCC screening. A cohort study in Cixian, China, demonstrated a significant reduction in both the incidence of esophageal cancer and mortality from esophageal cancer through 10 years of follow-up, with an HR of 0.61 and 0.45, respectively (Wei et al. 2015). A recent multicenter population-based cohort study with a larger sample size (113,340 screened individuals) involving six areas in China confirmed the effectiveness of a one-time endoscopic screening program. Through 10 years of follow-up, incidence and mortality rates of esophageal cancer were significantly reduced by 27% and 57%, respectively (Chen et al. 2021). Comparing 12 different ESCC screening methods in terms of cost in China, the authors suggested two screening strategies. In areas with low-income levels and limited health-care access, it was recommended that a patient will undergo one screening endoscopy at the age of 50 years. Subsequently, the patient will undergo surveillance at five years and three years for low-grade dysplasia and high-grade dysplasia, respectively. However, in areas with higher income levels and better health-care access, the recommendation was as follows: three screening endoscopies at five-year intervals starting at the age of 40 years, with subsequent equivalent surveillance of dysplasia (Yang et al. 2012). In regard to the screening endoscopic technique, chromoendoscopy with Lugol iodine staining is the gold standard to detect dysplasia or early ESCC. The sensitivity of Lugol chromoendoscopy in detecting high-grade dysplasia is excellent when compared with standard white-light endoscopy (96% vs. 62%) (Lao-Sirieix and Fitzgerald 2012). Some experts recommend endoscopic screening in the subgroup of patients with pre-existing high-risk conditions that predispose them to ESCC (e.g., HNSCC, tylosis, and achalasia), although there is no clear-cut, evidence-based guidance regarding the screening starting age and surveillance interval periods.

Surveillance for Barrett's Esophagus

Patients diagnosed with BE are recommended to undergo subsequent surveillance endoscopy so any dysplasia can be detected in a timely manner, that is, before the invasion of the submucosa, when the risk of lymph node metastases is significantly increased (Shaheen et al. 2016). The endoscopic technique is similar to the screening endoscopy as described earlier. In addition, a targeted biopsy should be performed for any visible or suspected dysplastic lesions, such as nodules or ulcers. If the biopsy indicates dysplasia, the finding should be confirmed by two pathologists (one of them should specialize in the gastrointestinal system).

In a large cohort study of BE patients (N = 29,536) in the United States, BE surveillance showed better EAC outcomes over a mean follow-up of five years. Compared with EAC patients diagnosed by non-BE surveillance endoscopy (n = 215), EAC patients from the BE surveillance program (n = 209) were diagnosed at an earlier stage (74.7% vs. 56.2%), had lower cancer-related mortality (34% vs. 54%), and had a trend to receive esophagectomy (51.2% vs. 42.3%) (El-Serag et al. 2016). The current BE surveillance guidelines vary slightly according to the gastrointestinal societies. Most of the recommendations are based on the degree of dysplasia and the length of BE. Those recommendations are summarized in Table 2.

Advanced Imaging Techniques in Barrett's Esophagus Surveillance

Detection for dysplasia might be hampered by inadequate sampling and interpretative error. To improve the detection rate of dysplasia in BE patients, several advanced endoscopic imaging techniques have been studied and meet the criteria for the preservation and incorporation of valuable endoscopic innovations (PIVI) released by the American Society of Gastrointestinal Endoscopy (ASGE), that is, per-patient sensitivity ≥ 90%, specificity ≥ 80%, and negative predictive value ≥ 98% for detecting high-grade dysplasia or EAC (Shaheen et al. 2016). One of those techniques is acetic acid chromoendoscopy. Acetic acid will trigger a chemical reaction with the proteins in the cytoplasm when sprayed onto the BE. Acetylation of the cytoplasmic proteins will then result in aceto-whitening of Barrett's mucosa. Non-neoplastic segments remain white, while neoplastic areas appear as red spots and are, therefore, easily identified and biopsied (Bhandari et al. 2017). Advantages of acetic acid chromoendoscopy are that it is a quick procedure and easy to learn and acetic acid is low in cost. A meta-analysis of nine prospective studies concluded a high diagnostic accuracy for detecting high-grade dysplasia and EAC in patients with BE. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 92%, 96%, 25%, and 8%, respectively (Coletta et al. 2016).

Virtual chromoendoscopy has been applied in BE surveillance, resulting in increased dysplastic lesion recognition, lesser biopsy, and reduced total cost (Pascarenco et al. 2016). Examples of virtual chromoendoscopy include narrow-band imaging (NBI) (optical chromoendoscopy), Flexible Spectral Imaging Color Enhancement (FICE) (digital chromoendoscopy), and i-Scan (digital chromoendoscopy), which are available on Olympus, FujiFilm, and PENTAX endoscopy systems, respectively. A meta-analysis found excellent results of a pooled sensitivity, specificity, and negative predictive value of 94.2%, 94.4%, and 97.5%, respectively (Thosani et al. 2016). A newer technique, namely confocal laser endomicroscopy (CLE), provides real-time diagnostic information at the cellular level. It requires intravenous fluorescence dye to excite the tissue. Typically, 2.5 mL of a 10% solution is administered immediately before the endomicroscopic examination (Pilonis et al. 2022). Probe-based CLE has a high specificity (of 98%) for detecting dysplasia and EAC but a sensitivity of only 67% (Shah et al. 2018). It is not widely used as yet due to its high cost and the fact that considerable training is required for the correlation between imaging and histology. Additionally, mild adverse events from dye injection have also been reported, including nausea, vomiting, mild epigastric pain, transient hypotension, and rash, at the site of injection (El-Serag et al. 2016).

Biomarkers for Barrett's Esophagus and Esophageal Adenocarcinoma

Since the annual progression rate from BE to high-grade dysplasia/EAC is low and endoscopy is costly and involves safety issues, there is a pressing need for risk stratification biomarkers for BE in order to predict the likelihood of BE to progress to high-grade dysplasia/EAC in a patient. Extensive studies have revealed some potential risk biomarkers, although none of them have been applied clinically as yet. Epigenetic alterations, such as DNA hypermethylation in the promoter region of genes, are among the potential biomarkers for BE and EAC. A retrospective study by the Early Detection Research Network (EDRN) found a few hypermethylated DNA markers (tissue-based assay) associated with an increased risk of progression from BE to high-grade dysplasia/EAC. These markers were hypermethylated p16 (OR: 1.74), RUNX3 (OR: 1.80), and HPP1 (OR: 1.77) (Schulmann et al. 2005). When these markers were combined with clinical features such as gender, BE's length, and histopathologic examination, a prediction model was able to stratify BE patients into low, intermediate, and high-risk groups (ROC curve: 0.8386 and 0.7910 for two-year and four-year prediction models, respectively) (Sato et al. 2008).

When assessing the role of miRNAs in risk stratification, multiple miRNAs, such as miR-15b, miR-25, miR-31, mi-93, miR-106b, miR-192, miR-194, miR-196a, miR-196b, miR-203, miR-205, miR-215, miR-375, and let-7c, have shown an association with the progression of BE along the metaplasia–dysplasia–carcinoma sequence (Bansal et al. 2011; Fassan et al. 2011; Leidner et al. 2012; Luzna et al. 2011; Maru et al. 2009; Revilla-Nuin et al. 2013; Smith et al. 2011). However, the efficacy of these markers is still suboptimal due to small-sample-sized studies, heterogenicity among studies, and non-standardized methods of detecting miRNAs (Grady et al. 2020).

Table 2 Barrett's esophagus surveillance guidelines.

BSG, 2013 & 2018	ACG, 2022	ASGE, 2019	ESGE, 2017	APC, 2016	AUS CPG, 2014
SURVEILLANCE METHODS					
Advanced imaging modalities such as chromoendoscopy, is not superior to standard white light endoscopy. Addition of p53 immunostaining may improve the diagnostic reproducibility of dysplasia in BE.	Recommends both white light endoscopy and chromoendoscopy. No recommendation on the use of p53 staining and TissueCypher in addition to standard histopathology examination.	Recommends chromoendoscopy over white light endoscopy. Do not recommend routine use of confocal laser endomicroscopy. Suggest using wide-area transepithelial sampling (WATS-3D) in addition to Seattle protocol.	Routine use of chromoendoscopy, optical chromoendoscopy, autofluorescence endoscopy, or confocal laser endomicroscopy is not advised.	Advanced endoscopic imaging techniques can be used to facilitate targeted biopsies and increase detection rate of dysplasia.	
SURVEILLANCE PROTOCOL FOR NON-DYSPLASTIC BARRETT'S ESOPHAGUS					
Surveillance not recommended in patients with IM at the cardia or those with irregular Z-line. BE < 3cm and without IM/dysplasia: repeat endoscopy. If no IM, discharge the patient from surveillance. BE < 3cm with IM: surveillance every 3–5 years. BE ≥ 3cm: surveillance every 2–3 years.	BE and without IM: repeat endoscopy in 1–2 years. BE < 3cm: surveillance every 5 years. BE ≥ 3cm: surveillance every 3 years.		BE < 1cm: no surveillance needed. BE ≥ 1cm and < 3cm: surveillance every 5 years. BE ≥ 3cm and < 10cm: surveillance every 3 years. BE ≥ 10cm: refer to BE expert center for surveillance endoscopy.	Surveillance every 3–5 years.	In columnar-lined esophagus without IM and dysplasia: a) < 1cm: no surveillance. b) ≥ 1cm and < 3cm: repeat endoscopy in 3–5 years. If still no IM, consider discharge. c) ≥ 3cm: surveillance every 2–3 years. BE < 3cm: surveillance every 3–5 years. BE ≥ 3cm: surveillance every 2–3 years.
MANAGEMENT OF DYSPLASIA AND EARLY CANCER					
Indefinite dysplasia					
Optimization of antireflux medication and repeat endoscopy in 6 months. If subsequent biopsies show no dysplasia, return to non-dysplastic BE protocol.	Intensification of antireflux medication (twice daily) and repeat endoscopy in 6 months. In persistent indefinite dysplasia, surveillance every 1 year.	Intensification of antireflux medication and repeat endoscopy.	Optimization of antireflux medication and repeat endoscopy in 6 months. If subsequent biopsies show no dysplasia, return to non-dysplastic BE protocol.		Optimization of antireflux medication and repeat endoscopy in 6 months. If repeat shows: a) No dysplasia: return to non-dysplastic BE protocol. b) Persistent indefinite dysplasia, repeat endoscopy in 6 months.

SURVEILLANCE METHODS					
Low grade dysplasia					
Repeat endoscopy in 6 months. If LGD is found, RFA should be offered. If RFA is not undertaken, continue surveillance every 6 months.	Repeat endoscopy in 6 months. RFA is recommended if persistent LGD. If not undertaken, repeat endoscopy at 12 months from diagnosis, and the annually thereafter.	Repeat endoscopy in 6 months. Endoscopic eradication therapy is recommended. If not undertaken, surveillance every year.	Repeat endoscopy in 6 months. If no dysplasia, surveillance interval can be broadened to 1 year. After 2 subsequent endoscopies negative for dysplasia, return to non-dysplastic BE protocol. If LGD is found on subsequent endoscopies, RFA should be offered.	Consider treatment or surveillance. If for treatment, endoscopic resection for all visible lesions. RFA should be considered in the absence of focal lesions. If for surveillance, repeat endoscopy in 6 months to confirm LGD.	Surveillance every 6 months. If 2 consecutive 6-monthly endoscopies show no dysplasia, consider less frequent surveillance follow up. Consider endoscopic ablation especially where LGD is definite, multifocal, and present more than one occasion.
High grade dysplasia & Barrett's related adenocarcinoma					
HGD/intramucosal cancer without visible lesions: endoscopic ablative technique – RFA has a better safety profile with comparable efficacy. Dysplasia associated with visible lesions and T1a adenocarcinoma: Endoscopic resection followed by ablation. Good prognosis T1b adenocarcinoma, but at high risk of surgery: endoscopic therapy can be offered.	Dysplasia associated with visible lesions and T1a adenocarcinoma: Endoscopic resection followed by ablation. Good prognosis T1b adenocarcinoma, but at high risk of surgery: endoscopic therapy can be offered.	Endoscopic eradication therapy or alternatively surveillance every 3 months.	T1a adenocarcinoma: endoscopic resection. T1b adenocarcinoma: endoscopic resection may be a valid alternative to surgery if the endoscopic resection specimen meets all these criteria: a) submucosal invasion < 500um. b) well or moderate differentiated. c) absence of lymphatic/blood vessels invasion. d) absence of tumor infiltration in deep resection margin.	Dysplasia associated with visible lesions and T1a adenocarcinoma: Endoscopic resection followed by ablation.	Dysplasia associated with visible lesions and T1a adenocarcinoma: endoscopic resection followed by BE eradication (RFA, cryotherapy). Selected patients with T1b early adenocarcinoma may also be offered endoscopic resection, only if esophagectomy is not indicated.

(Recommended biopsy is according to Seattle protocol, i.e., quadrantic biopsy every 2cm for non-dysplastic BE, and every 1cm for dysplastic BE).

ACG, American College of Gastroenterology; APC, Asia-Pacific Consensus; ASGE, American Society of Gastrointestinal Endoscopy; AUS CPG, Australian Clinical Practice Guidelines; BE, Barrett's esophagus; BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation

Among the altered proteins studied in the risk stratification of BE, altered TP53 has shown an encouraging result. In a recent retrospective study (n = 561 BE patients), abnormal p53 expression was highly correlated with the TP53 mutation status (90.6% agreement) and significantly associated with the progression of BE. However, in a subsequent prospective validation cohort (n = 1487 BE patients), only 49.7% of the progressors had altered TP53 immunostaining (Redston et al. 2022). Although none of BE guidelines have recommended routine testing of TP53 as part of risk stratification, the BSG guideline does have a grade B recommendation to test the immunostaining of TP53 in cases with indeterminate dysplasia (Fitzgerald et al. 2013).

Prevention

Primary prevention of esophageal cancer involves controlling the modifiable risk factors, while secondary prevention primarily aims to prevent neoplastic progression of the precursor lesions. For EAC, treatment of the GERD symptoms, cessation of smoking, and weight loss to address obesity are important preventive interventions. Although nearly half of the patients diagnosed with EAC do not have classic GERD symptoms (Barb et al. 2007), the severity and chronicity of GERD symptoms remain strong indicators for progression toward EAC. In a population-based case-control study, the presence of reflux symptoms increased the risk of EAC (OR: 3.61). This risk was higher with the presence of hiatus hernia (which signifies silent reflux) (OR: 5.85) and the highest in cases with both reflux and hiatus hernia (OR: 8.11) (Wu et al. 2003). Therefore, the treatment of GERD with acid suppression is vital to prevent the chemical irritation of the distal esophagus by gastric acid and bile. Proton pump inhibitors (PPIs) effectively control GERD symptoms and potentially reduce the risk of high-grade dysplasia and EAC in patients with BE. A meta-analysis of seven observational studies showed a 71% reduction in the risk of high-grade dysplasia and EAC (OR: 0.29) with PPI therapy (Singh et al. 2014a). A recent prospective study (AspECT trial) with a median follow-up of 8.9 years has demonstrated the superiority of 40 mg esomeprazole over 20 mg esomeprazole in reducing the incidence of dysplasia and neoplastic lesions in patients with BE (Jankowski et al. 2018) PPI. Although PPIs are generally safe, possible long-term side effects, such as osteoporosis, pneumonia, infectious diarrhea, and dementia, may preclude its use as a chemopreventive agent. BSG guidelines recommend the use of PPIs for symptom control only. However, recent ACG guideline 2022 recommends once-daily PPI therapy in patients with BE (Shaheen et al. 2022). In addition, the AspECT trial demonstrated a significant effect of low dose aspirin 300 mg, to decrease progression to high grade dysplasia (Jankowski et al. 2018). This was also one of the first trials to show an additive effect of two chemoprevention agents, high dose twice a day PPI and once a day aspirin, to work synergistically to prevent death and high-grade dysplasia. This trial cohort is being followed up in the AspECT Excel trial to see if both agents need longer than nine years' use to prevent the development of EAC.

Since obese individuals are likely to have GERD, it is wise to encourage the patients to reduce weight and adopt a healthier dietary style. Randomized controlled trials have shown that weight loss and visceral fat loss are associated with improved GERD symptoms and a reduction in esophageal exposure to acid (Mathus-Vliegen and Tytgat 1996; Mathus-Vliegen and Tygat 2002). A prospective population-based cohort study in Norway (the HUNT study) examined the association between weight loss and reduction in GERD symptoms in 29,610 individuals. The authors concluded that weight loss is dose-dependently associated with both the reduction in GERD symptoms and an increase in treatment success with anti-reflux medication (OR: 1.98 and 3.95, respectively) (Ness-Jensen et al. 2013). Concerning anti-reflux surgery, the BSG guideline made a statement that "it is not superior to the pharmacological acid suppression for the prevention of neoplastic progression of BE, and therefore should only be considered in patients with poor or partial symptomatic response to PPIs" (Fitzgerald et al. 2013).

Notably, a proportion of obese patients have difficulty reducing their body weight despite following dietary and lifestyle modification advice. Bariatric surgery is an effective intervention for weight reduction, and the two most frequently performed procedures are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). There is no official statement made either for or against bariatric surgery as a preventive measure for BE/EAC. However, it should be noted that although both RYGB and SG have equivalent and good outcomes in terms of weight reduction (Peterli et al. 2018; Salminen et al. 2018), SG might worsen preexisting GERD symptoms or even induce de novo GERD symptoms (Felsenreich et al. 2017; Genco et al. 2017; Mandeville et al. 2017). In fact, a recent meta-analysis of 46 studies found a 19% increase in post-operative GERD, a 23% increase in de novo reflux, a 28% increase in esophagitis, and an 8% increase in BE in patients who had undergone SG (Yeung et al. 2020).

A few studies have looked at the role of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and statin as chemoprevention for EAC. A few observational studies have demonstrated a protective effect of aspirin and NSAIDs against BE progression to high-grade dysplasia/EAC (Corley et al. 2003; Gammon et al. 2004; Liao et al. 2012). In the AspECT trial, aspirin was found to lengthen the time to reach the combined endpoint of death (mortality from any cause, EAC, or high-grade dysplasia), but only when patients using other NSAIDs were censored. The study also revealed that a combination of 40 mg esomeprazole with aspirin had a stronger effect as compared to 20 mg esomeprazole without aspirin (Jankowski et al. 2018). However, the primary outcome measured was the combined endpoint of deaths, and the study did not demonstrate any significant results for cancer-related outcomes. However, they did reduce high grade dysplasia and death from all causes including aspiration related pneumonia. Due to unclear benefit/risk profile and a lack of concrete evidence, BSG and ACG have made no recommendation regarding the use of aspirin and other NSAIDs as chemoprevention for EAC.

A meta-analysis of 13 studies demonstrated a significant pooled reduction (28%) in the incidence of EAC among statin users. The benefit was further increased (41% in EAC incidence reduction) in a subgroup of patients with BE (in 5 studies) (Singh et al. 2013b). However, the authors acknowledged that there was considerable heterogeneity among studies. In a nested case-control study among US veterans with BE, statin use was associated with a decreased risk of EAC with an adjusted OR of 0.65 (Nguyen et al. 2015). Although currently available evidence from observational studies indicates the protective effect of statin in preventing BE progression, the sole use of statin as chemoprevention is currently not routinely recommended.

Similarly, the primary prevention of ESCC would revolve around avoiding the precipitating risk factors, such as cigarette smoking, excessive alcohol intake, and high intake of pickled foods and hot drinks. Patients should be encouraged to adopt a healthier lifestyle, with increased consumption of fruits and vegetables. The evidence of PPIs, aspirin, NSAIDs, and statin as chemoprevention for ESCC is conflicting and scanty (Alexandre et al. 2016; Arai et al. 2021; Nielsen et al. 2012), and therefore their use is not advocated for now.

Gastric Cancer

Risk Factors for Gastric Cancer

Non-modifiable Risk Factors

Risk factors for gastric cancer vary according to the tumor location within the stomach, that is, cardia and non-cardia regions. Common non-modifiable risk factors for both types of gastric cancers include advanced age, male gender, and family history. Epidemiological data from the United States showed that a higher proportion of individuals (70%) diagnosed with gastric cancers were in the age group of 55–84 years (Karimi et al. 2014). Males have a predilection, with a five- and two-fold higher risk for cardia and non-cardia gastric cancer, respectively, as compared to females (Brown and Devesa 2002). This male predominance might be explained by experimental and observational studies that have shown a potential protective effect of estrogens and the harmful effect of anti-estrogen drugs, such as tamoxifen, on the development of gastric cancer. Additionally, women seem to develop gastric cancer at a similar rate as men after menopause, but with a 10–15-year lag (Camargo et al. 2012; Derakhshan et al. 2009; Karimi et al. 2014; Sheh et al. 2011).

Race or ethnicity poses an important non-modifiable risk factor for gastric cancer. Data from the United States registry (Surveillance, Epidemiology, and End Results Registry 1992–2009) showed a nearly doubled incidence rate in non-white Americans compared with white Americans: whites 7.4/100,000; Asian/Pacific Islanders 15.6/100,000; Africans 12.8/100,000; Hispanics 12.9/100,000 (Lui et al. 2014). Within the Asian American subgroup, Korean and Japanese Americans had a much higher incidence rate (Kim et al. 2016). Globally, four countries that have a high gastric cancer incidence (defined as an age-standardized rate ≥20/100,000) are South Korea (39.6/100,000); Mongolia (33.1/100,000); Japan (27.5/100,000); and China (20.7/100,000) (Rawla and Barsouk 2019).

Although most gastric cancer cases are sporadic, in 10% of the cases, the presence of family history is observed. The odds ratio for the risk of developing gastric cancer in individuals with first-degree relatives with gastric cancer ranges from 2 to 10 (La Vecchia et al. 1992; Palli et al. 1994; Shin et al. 2010; Yaghoobi et al. 2010). A small percentage of gastric cancer cases with a positive family history are thought to arise from the hereditary syndrome. A few hereditary syndromes are associated with an increased risk of gastric cancer, with the highest risk being carried by hereditary diffuse gastric cancer (HDGC) syndrome. It is characterized by autosomal dominant inheritance, with a germline mutation in the CDH1 tumor suppression gene at chromosome 16q22 that encodes E-cadherin (Rawla and Barsouk 2019). HDGC syndrome is associated with an estimated 70% lifetime risk of gastric cancer in men and a 56% risk in women (frequently early onset, before the age of 40 years) (Hansford et al. 2015). In addition, there is a 50% lifetime risk of lobular breast cancer and an increased risk of signet-ring cell colorectal cancer (Roberts et al. 2019). Other syndromes associated with an increased gastric cancer risk include Peutz–Jeghers syndrome (29% lifetime risk), juvenile polyposis (21% lifetime risk), Lynch syndrome (6–13% lifetime risk), hereditary breast/ovarian cancer syndrome (2.6–5.5% lifetime risk), and familial adenomatous polyposis (0.5–2% lifetime risk) (Chun and Ford 2012).

Modifiable Risk Factors

The most important risk factor for gastric cancer (and it is modifiable) is *Helicobacter pylori* infection. In 1994, *H. pylori* was classified as a class 1 carcinogen by the International Agency for Research on Cancer (IARC), given its pathogenic role in the development of gastric cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1994). Colonization and subsequent infectivity of *H. pylori* in the stomach would trigger gastric inflammation and if left untreated would lead to chronic gastritis. Over time, this condition can progress to gastric atrophy and intestinal metaplasia, two important precursors of gastric cancer. A meta-analysis of 12 studies revealed a higher risk of non-cardia gastric cancer with the *H. pylori* infection (OR: 2.97) compared with cardia gastric cancer (OR: 0.99) (Helicobacter and Cancer Collaborative Group 2001). Although gastric cancer is detected in approximately 1% of individuals with *H. pylori* infection (de Vries and Kuipers 2007), more than 90% of individuals diagnosed with gastric cancer had a history of *H. pylori* infection (Kato et al. 2007). The type of *H. pylori* strain and the duration of the infection have also been shown to further influence the risk of gastric cancer. Individuals with the *cagA* positive strain of *H. pylori* (Azuma et al. 2004; Matos et al. 2013) and a history of childhood *H. pylori* infection (Kikuchi et al. 1995; Mitchell et al. 1992) are at a higher risk of getting gastric cancer.

Other modifiable risk factors for gastric cancer, although less significant than *H. pylori* infection, are dietary intake, cigarette smoking, alcohol consumption, and obesity. Dietary patterns implicated in the development of gastric cancer include moderate–high salt intake (relative risk: 1.41–1.68) (D'Elia et al. 2012) (HR: 2.67) (Shikata et al. 2006), pickled/smoked/dried foods (Tsugane S. 2005), a Western/unhealthy diet rich in starchy and fatty foods (OR: 1.51) (Bertuccio et al. 2013), and meat intake (association between meat intake and non-cardia gastric cancer, HR: 3.52 for total meat intake, 1.73 for red meat, and 2.45 for processed meat) (Gonzalez et al. 2006). Consumption of fruit, vegetables, and vitamin C (HR: 0.5) seems to provide a protective effect against gastric cancer (Larsson et al. 2006; Riboli and Norat 2003; You et al. 1988).

A meta-analysis of 42 studies showed an increased risk of both cardia (relative risk: 1.87) and non-cardia (relative risk: 1.60) gastric cancers with cigarette smoking (Ladeiras-Lopes et al. 2008). Another meta-analysis of alcohol consumption and risk of gastric cancer showed a dose-dependent relationship, albeit the risk was much lower compared to dietary factors and cigarette smoking. The pooled relative risk for heavy alcohol drinkers (≥4 drinks/day) was 1.20, as compared to casual alcohol drinkers, 1.07 (Tramacere et al. 2012). Regarding obesity, a meta-analysis of 10 cohort studies revealed an increased risk of gastric cancer with excess body weight (BMI ≥ 25), with an OR of 1.22. When stratified according to the subgroup, its risk seems to be significant in gastric cancer arising from the cardia region (OR: 1.55) rather than from the non-cardia region (1.18) (Yang et al. 2009).

Precursor Lesions: Atrophic Gastritis and Intestinal Metaplasia

Atrophic gastritis (AG) and IM are well-known precursors of gastric cancer, as proposed in Correa's cascade model (Correa 1992). Both terms are defined histologically, with AG characterized by a loss of gastric glandular cells due to chronic inflammation of gastric mucosa (predominantly associated with *H. pylori* infection) or other causes, such as environmental factors and autoimmunity (Crafa et al. 2018). Atrophy can present as focal, multifocal, or diffuse patterns in the stomach. The loss of glandular cells in AG is usually replaced by IM, which is an intestinal-type epithelium lined by Paneth, goblet, and absorptive cells (Park ad Kim 2015).

A prospective population-based cohort study in the Netherlands showed that the incidence of gastric cancer increased as the premalignant gastric lesions progressed. Among individuals with atrophic gastritis, the annual incidence of gastric cancer was 0.1%, followed by 0.25% for individuals with intestinal metaplasia, 0.6% for individuals with mild–moderate dysplasia, and 6% for individuals with severe dysplasia (de Vries et al. 2008). In terms of the relative risk of gastric cancer in patients with *H. pylori* infection and AG, the risk was higher in moderate (relative risk: 1.7) and severe atrophies (relative risk: 4.9) as compared to none/mild atrophy (Uemura et al. 2001). The same cohort study also demonstrated a significantly higher risk of gastric cancer in the presence of gastric IM (relative risk: 6.4) (Uemura et al. 2001). A large-population-based study from Germany replicated the gastric cancer risk from these precursor lesions (hazard ratio of 32.4 for the combination of AG and *H. pylori* infection) (Chen et al. 2016). IM can be subdivided histologically into complete and incomplete types. The incomplete type of IM shows a higher risk of progression to gastric cancer (relative risk of 4–11 when compared to the complete type) (Gonzalez et al. 2013).

Screening

Population-based screening for gastric cancer is not advocated, except for high-incidence countries. Indeed, Japan and South Korea are the only two countries implementing a nationwide screening program for gastric cancer at the moment. Japan's screening program was initiated regionally in 1960 and formally enrolled nationwide in 1983 (Li et al. 2019). Fifty years of age and above is used as the cut-off screening age, and at the early stage of the program, individuals were screened by radiography, that is, barium meals and fluorography. From 2015 onward, the Japanese guidelines recommended the use of both radiographic and endoscopic techniques for the screening, because of increasing evidence of the efficacy of endoscopy as a screening method (Hamashima 2018). South Korea launched its nationwide screening program in 1999 and adopted a similar screening strategy, albeit at a lower screening age, of 40 years and above (Jun et al. 2017).

The screening program in these high-incidence countries has shown promising outcomes in support of its effectiveness. Gastric cancer was detected at earlier stages during the screening period (40% in Japan and 46–67% in Korea) (Lee et al. 2006; Mizoue et al. 2003). The risk of gastric cancer was also found to be lower in the screened individuals compared to the unscreened ones (relative risk: 0.52–0.72 in Japan and 0.79 in Korea) (Hamashima 2018). Most importantly, recent data from Japan have shown a downward trend in the age-adjusted incidence and mortality rates (Sekiguchi et al. 2021).

In China, rather than conducting a mass-screening program for the early detection of gastric cancer, they follow a modified high-risk population strategy, in which individuals aged 40–69 years living in selected high-risk regions are invited for screening. Examples of such areas are Yangzhong (initiated in 2006), Linqu County in Shandong (2008), Zhuanghe County in Liaoning (2008), Huai River Basin (2008), and Wuwei County in Gansu (2010) (Fan et al. 2021). Most studies evaluating the effectiveness of screening programs in China have shown favorable outcomes, including increased detection of early gastric cancer and reduced incidence and cancer-specific mortality rates (Chen et al. 2021; Wei et al. 2015; Zhang et al. 2018). The first ever Chinese multicenter cluster-randomized trial of endoscopic screening for esophageal and gastric cancers was launched in 2015 and is currently in the follow-up phase. The initial baseline data were encouraging, in which the diagnostic yield of both cancers was higher in high-risk areas than in non-high-risk areas (esophagus: 0.9% vs. 0.1%, stomach: 0.9% vs. 0.3%). The same went for the early detection rate (esophagus: 92.9% vs. 53.3%; stomach: 81.5% vs. 33.3%) (Zeng et al. 2020). Hopefully, the end-of-trial analysis will provide the much-awaited result of the effectiveness of population-based screening of esophageal and gastric cancers.

Endoscopic screening and endoscopic surveillance for individuals with the gastric-cancer-associated hereditary syndrome are recommended, given the increased lifetime risk for gastric cancer. For HDGC, endoscopic screening is defined for individuals who have undergone endoscopy who do not know their mutation status or do not have pathogenic CDH1 mutation. Endoscopic surveillance is termed for individuals with CDH1 mutation positivity undergoing endoscopy (van der Post et al. 2015). For individuals with HDGC who have undergone endoscopic screening, the guideline recommends repeating endoscopy annually if the gastric biopsy is negative for signet ring cell carcinoma. In individuals with positive CDH1 mutation, prophylactic gastrectomy at the ages of 20–30 years is advocated. However, if gastric biopsy indicates the presence of signet ring cell carcinoma and surgery is delayed or refused, annual endoscopic surveillance is recommended, and prophylactic gastrectomy should be re-emphasized (Pilonis et al. 2021). Identifying the subtle gastric lesions in HDGC patients is endoscopically challenging. The rate of a diagnosis miss is as high as 60%, even with the use of high-definition endoscopy and NBI (Pilonis et al. 2021). During endoscopy, the stomach should be meticulously inspected, with sufficient endoscopic time spent (30 minutes), but before the endoscopy, the stomach should be thoroughly cleansed with saline and anti-foaming agent. An extensive mapping biopsy protocol is recommended, with 5 biopsies in the antrum, the transitional zone, the fundus, and the cardia and 10 biopsies in the gastric body (Blair et al. 2020).

Regarding other hereditary syndromes, Li et al. recommended the following (Li et al. 2019):

1 Peutz–Jeghers syndrome: The first screening OGD should be performed at the age of eight years and continued endoscopic surveillance conducted every 2–3 years if gastric polyps are present. If no gastric polyps are identified on the first OGD, the next endoscopic surveillance should be at the age of 18 years and continued thereafter. After the age of 50 years, patients are advised to undergo annual endoscopic screening.

2 Juvenile polyposis syndrome: The first screening OGD should be performed in the mid-teens or when symptomatic. If no polyps are detected, endoscopic surveillance is recommended every three years. In the presence of a few gastric polyps, patients should go for annual endoscopic surveillance. Prophylactic total gastrectomy is recommended if multiple polyps are found.

3 Lynch syndrome: First screening OGD is recommended at the age of 40 years and should be repeated every three years. However, the latest BSG and ESGE guidelines do not recommend routine endoscopic surveillance for Lynch syndrome. (Monahan et al. 2020; van Leerdam et al. 2019).

4 Li–Fraumeni syndrome: As per National Comprehensive Cancer Network guidelines, the first screening OGD should be performed at the age of 25 years or 5 years before the earliest known gastric cancer. A surveillance interval of 2–5 years has been suggested (Daly et al. 2021).

Screening Methods for Gastric Cancer

Screening modalities for gastric cancer include radiography, endoscopy, and serology testing. Barium meals and fluorography have been used at the early stage of the screening program in Japan and South Korea. Barium contrast is used to delineate the gastric lining, and if any suspicious lesions are detected radiographically, patients will be advised to proceed with endoscopy. Although this technique is non-invasive, widely available, and uncostly, the patient tolerance for the procedure is low, affecting the participation rate in Japan (Hamashima 2014). In a large-population-based study in Korea, the sensitivity and specificity of barium meals were found to be 36.7% and 96.1%, respectively, (Choi et al. 2012), while in Japan, they were 89.3% and 91.4%, respectively (Hamashima et al. 2015). Nowadays, this radiographic modality in Japan and Korea has been largely replaced by endoscopy due to its better efficacy.

Evidence of the efficacy of endoscopic screening for gastric cancer, as opposed to radiography, is plenty. Endoscopic screening exhibits a higher detection rate of gastric cancer (Matsumoto 2007; Tashiro et al. 2006), higher sensitivity and specificity (Daly et al. 2021; Hamashima 2014), and a higher reduction rate in mortality and is more cost effective (Cho et al. 2013) and has a better acceptance rate as compared to radiographic screening (Lee et al. 2015). A thorough endoscopic inspection of the gastric mucosa is paramount to increase the detection rate of precursor lesions and early gastric cancer. Endoscopically, AG features that should be sought out include pale mucosa, loss of gastric folds, prominence of vessels, and presence of atrophic border (Kohoutova et al. 2021). Gastric IM is much more difficult to appreciate. The appearance of gray-white mildly elevated plaques surrounded by patchy pale areas on standard white-light endoscopy and “marginal turbid band with light blue crest” on magnifying advanced imaging are indicative of gastric intestinal metaplasia (Banks et al. 2019; Kohoutova et al. 2021) (see Figure 2). Expert recommendations for optimal endoscopic practice include (Kohoutova et al. 2021):

1 Combined use of high-resolution white-light endoscopy and magnifying NBI
2 Application of mucolytic/defoaming agents to achieve optimal mucosal visualization
3 A minimum inspection time of seven minutes
4 Procurement of endoscopic images after careful inspection
5 Multiple gastric biopsies if there is a suspicion of atrophic gastritis and intestinal metaplasia.

Two serologic screening procedures for gastric cancer that have been explored clinically are *H. pylori* serology and serum pepsinogen (PG). The role of *H. pylori* serology as a stand-alone screening test is limited due to its low sensitivity and inability to detect precursor lesions. An *H. pylori* infection has a strong link with the development of gastric cancer. However, previous studies have shown that the gastric cancer risk is actually higher in *H. pylori*-negative patients. This paradox probably can be explained by the spontaneous disappearance of *H. pylori* as the chronic gastritis progresses to AG and IM, making the gastric microenvironment nonconducive (Yoon and Kim 2015). There are two types of PG, PG I (produced by the chief and mucous neck cells) and PG II (also additionally secreted by the pyloric and Brunner's glands) (Choi et al. 2012). As the severity of atrophic gastritis increases, the PG I level decreases but the PG II level remains stable (Park and Kim 2015). As a result, a PG I value of <70 ng/mL and a PGI/II ratio of <3 have been used as cut-offs for gastric cancer screening, with a sensitivity and specificity of 84.6% and 73.5%, respectively (Kitahara et al. 1999; Sugano K. 2015).

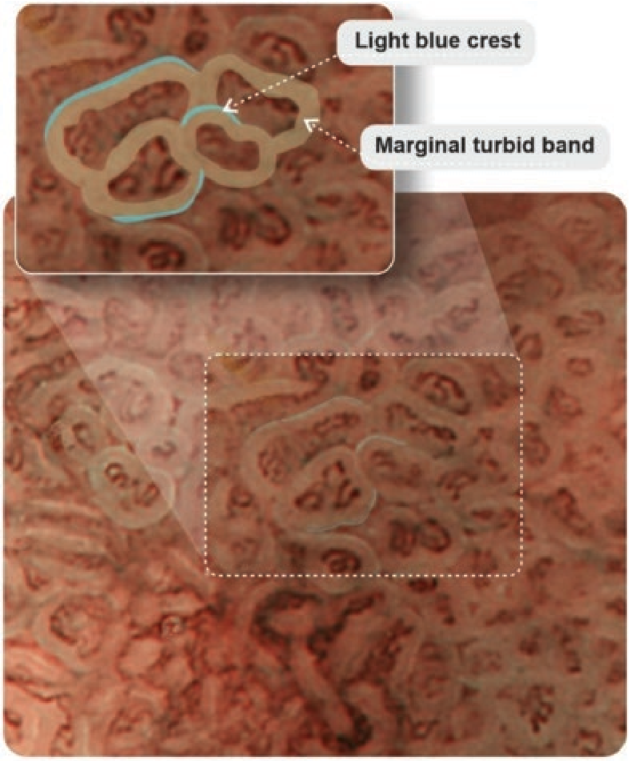

Figure 2 Using image-enhanced and magnification endoscopy, features of gastric intestinal metaplasia include light blue crest and marginal turbid band (Kohoutova et al. 2021/ MDPI/CC BY 4.0).

Multiple Japanese studies have evaluated the combination of *H. pylori* serology and serum PG as a non-invasive screening test. This strategy is known as the ABC method (implemented in Nishitokyo city since 2011) (Yamaguchi et al. 2016). Patients are stratified into four groups according to the positivity/negativity of the *H. pylori* serology and PG I with PGI/II ratio values. In the negative group, no further testing is required. In the other three groups, *H. pylori* eradication therapy is recommended, followed by surveillance endoscopy every three years (*H. pylori*-positive, PG-negative group), two years (*H. pylori*-positive, PG-positive group), or annually (*H. pylori*-negative, PG-positive group). These surveillance intervals vary according to the gastric cancer risk, as shown by HR of 1.1 to 4.2, 6.0 to 11.23, and 8.2 to 14.81, respectively (Kishikawa et al. 2015).

Biomarkers for Gastric Cancer

Early detection of gastric cancer is challenging, mainly due to either individuals' lack of symptoms or the presence of non-specific gastrointestinal symptoms. Therefore, many studies have been conducted to identify novel biomarkers that could aid in the screening and surveillance of precursor lesions/early gastric cancer, as well as in prognostication and predicting treatment response. A recent systematic review has identified a total of 185 novel biomarkers for gastric cancer that have been sufficiently validated but need further evaluation in the low-prevalence population. In terms of the type of biomarkers in gastric cancer, the most commonly studied category is microRNA and other RNAs (n = 80), followed by autoantibodies and other immunological markers (n = 52), proteins (n = 44), and circulating tumor DNA (n = 7). Apart from serum PG, other biomarkers are yet to be used in clinical practice and certainly need further evaluation and validation (Calanzani et al. 2021).

Surveillance

Regarding endoscopic surveillance intervals for AG and IM, the Japanese and Koreans do not specifically recommend any surveillance intervals, except for the existing intervals of screening for gastric cancer every two years (either with radiography or endoscopy) and conducting endoscopy surveillance at three-, two-, and one-year intervals according to the ABC method. Nevertheless, other major gastrointestinal societies, such as AGA (Gupta et al. 2020; Shah et al. 2021), BSG (Banks et al. 2019), and the European Society of Gastroenterology (ESGE) (Pimentel-Nunes et al. 2019), do provide recommendations on the surveillance of these neoplastic precursor lesions, albeit with slight variations among them. In general, adherence to the Sydney biopsy protocol is recommended; two biopsies from the gastric antrum, two from the body (at the lesser and greater curvatures), and one from the incisura. In addition, all individuals undergoing endoscopy should be tested for *H. pylori* infection and treated if positive, with subsequent testing to confirm eradication.

Individuals with extensive AG/IM, defined as the involvement of antrum and corpus, are recommended to undergo endoscopic surveillance every three years. Surveillance is not recommended if the finding is only limited to the antrum. However, with any additional risk factors, such as a family history of gastric cancer, an incomplete subtype of intestinal metaplasia, and persistent *H. pylori* infection, such individuals are advised to undergo surveillance every three years as well, given the perceived high risk for gastric cancer. ESGE, along with other European Societies, in 2019 guidelines (Pimentel-Nunes et al. 2019), further recommends a shorter surveillance interval (1–2 years) in individuals with extensive AG/IM and the presence of a family history of gastric cancer. In individuals with non-visible dysplasia, BSG recommends an immediate repeat endoscopy for extensive gastric mapping with biopsy (Banks et al. 2019). If persistent dysplasia is detected, both BSG and European guidelines recommend surveillance in 1 year and 6 months for low-grade and high-grade dysplasia, respectively. BSG further recommends a multidisciplinary team discussion in the case of non-visible, high-grade dysplasia.

An expert review by AGA additionally provides a few best practices for autoimmune atrophic gastritis. Individuals with the clinical suspicion of pernicious anemia should undergo endoscopy with multiple biopsies to establish the diagnosis of corpus-predominant atrophic gastritis. As part of the endoscopic screening for AG/IM/dysplasia, they should also be endoscopically screened for type 1 neuroendocrine tumors. No clear-cut endoscopic surveillance interval for autoimmune atrophic gastritis has been suggested and, therefore, the frequency of endoscopy should be based on shared decision-making with the patients. However, if a small endocrine tumor (<1 cm) is detected, it should be resected and endoscopic surveillance performed every 1–2 years (Shah et al. 2021).

Prevention

The most important primary prevention step for gastric cancer is the treatment of *H. pylori* infection and the subsequent confirmation of its eradication. A meta-analysis of seven randomized trials (6695 participants) showed a larger proportion of gastric cancer cases in untreated individuals vs. treated individuals (56/3307 (1.7%) vs. 37/3388 (1.1%)). The risk of gastric cancer was also reduced in *H. pylori*-treated individuals, with a relative risk of 0.65 (4- to 10-year follow-up) (Fuccio et al. 2009). One randomized placebo-controlled trial was performed in China involving 1630 healthy carriers of *H. pylori* infection (988 participants had precancerous lesions). Overall, no significant difference was detected in the incidence of gastric cancer in both groups after a mean follow-up of 7.5 years: 7 cases in the treatment group vs. 11 cases in the placebo group, p = 0.33. However, in a subgroup analysis after excluding the participants with precancerous lesions, eradication of *H. pylori* significantly decreased the development of gastric cancer, that is, 0 cases in the treatment group vs. 6 cases in the placebo group, p = 0.02 (Wong et al. 2004).

Another randomized controlled trial (the Shandong Intervention Trial) in a high-risk region in China (Linqu County) has shown a significant reduction in gastric cancer, by 39%, with the *H. pylori* treatment during the follow-up period of 15 years (Ma et al. 2012). In the treatment group, the *H. pylori* eradication rate was reported as 72.9%. This trial also demonstrated the feasibility of conducting a large-community-based *H. pylori* screening and eradication program. In this trial, 53.1% of the county's eligible population (total of 347,811 individuals aged 25–54 years) participated, indicating a good acceptance among the residents (Pan et al. 2016). Another important study was recently conducted by the Taiwanese group on a high-risk population dwelling on Matsu Islands. In this cohort study, a very good coverage for mass screening and eradication had been achieved (85.5%), with a subsequent fall in the prevalence rate of *H. pylori* to 15% from 64.2%. The long-term benefits included a reduction in gastric cancer incidence by 53%, a reduction in gastric cancer mortality by 25%, and a significant decline in prevalence rates of premalignant gastric lesions, that is, atrophic gastritis and intestinal metaplasia, from 7.1% to 0 and from 11.8% to 1.8%, respectively. Interestingly, when the decreasing trends were extrapolated, a greater reduction of 68% in gastric cancer incidence and of 39% in mortality rate, would be expected by 2025 (Chiang et al. 2021).

Currently, in the majority of the countries, *H. pylori* screening strategy is mainly opportunistic based. In some high-risk gastric cancer regions, community-based *H. pylori* screening and eradication programs have already been launched (Chiang et al. 2021; Lee et al. 2013; Pan et al. 2016). In an ideal situation, a vaccine against *H. pylori* probably is the best option to ensure mass *H. pylori* eradication. However, the progress of such vaccines is slow and still uncertain, with most of the vaccines currently being developed are still in the preclinical stage (Sutton and Boag 2019).

Since cigarette smoking, alcohol consumption, obesity, and dietary factors have been associated with gastric cancer to some extent, individuals should be advised to practice a healthy lifestyle, although the evidence for these preventive measures is still lacking. The role of aspirin, NSAIDs, and statin as chemoprevention in gastric cancer has also been explored in multiple observational and case-control studies. Most studies showed a risk reduction of 30 – 50% (Zakko et al. 2017). However, due to the heterogenicity of these studies, lack of robust study design, and an unclear benefit/risk profile, their sole usage as gastric cancer chemoprevention is not recommended for now.

Summary

Upper GI malignancies are among the most prevalent cancers globally and have high disease burden with significant negative impacts on public health. As the first step toward tackling their rising incidence, it is critical to recognize the potential associated risk factors, such as chronic GERD symptoms, obesity, high intake of salty/pickled foods, and *H. pylori* infection, and take subsequent preventive measures. More robust, high-quality study designs are needed to evaluate the efficacy and cost-effectiveness of existing screening and surveillance programs for BE, ESCC, and gastric cancer. Similarly, more evidence and systematic guidelines are needed for the screening and surveillance strategy in high-risk groups in the low- and intermediate-incidence population. Endoscopy is a great screening tool, and with the emergence of advanced imaging technologies, it will definitely improve the detection rate of precursor lesions/early cancers. Nevertheless, less invasive tools and non-invasive biomarkers are needed for a better screening/surveillance approach for accurate risk stratification so that a well-informed prognosis can be offered to the patients.

Key Take Home Messages

- Majority of gastrointestinal societies in the West advocate the endoscopic screening for Barrett's esophagus in high-risk individuals; having chronic GERD symptoms with ≥3 of the following risk factors: male, ≥50 years, Caucasian, smoking, obesity, and family history of Barrett's esophagus or esophageal adenocarcinoma.
- Mass screening for esophageal squamous cell carcinoma and gastric cancer are limited to high-incidence countries/regions. Screening for esophageal squamous cell carcinoma is implemented in certain regions in China, while for gastric cancer, screening program has been established in Japan, South Korea, and certain regions in China.
- Optimal endoscopic practices are very important when conducting surveillance endoscopy. For Barrett's esophagus surveillance, endoscopists are required to adhere to Seattle's biopsy protocol and recommended to apply chromoendoscopy (dye or virtual) to enhance dysplasia detection. For atrophic gastritis/intestinal metaplasia, Sydney biopsy protocol is recommended while maintaining maximum mucosa visualization by applying magnifying narrow band imaging, usage of defoaming agent, and adequate inspection time.
- Tackling the modifiable risk factors forms the important step in preventing upper gastrointestinal cancers. Treating the obesity and gastroesophageal reflux disease would reduce the incidence of esophageal adenocarcinoma while adopting healthier lifestyle such as stopping tobacco smoking, high fruits/vegetables consumption and low pickled foods/hot drinks intake might prevent the occurrence of esophageal squamous cell carcinoma. In addition, individuals should be screened for *Helicobacter pylori* infection and offered eradication therapy in order to prevent gastric cancer.

Areas for Further Research

- Novel biomarkers for screening, surveillance, and prognostication of upper gastrointestinal precursor lesions/cancers are in dire need. To date, multiple biomarkers have been explored, but lack of clinical validation.
- More randomized trials are needed in regard to the application of image enhanced endoscopy incorporating an artificial intelligence for early detection of pre-cancerous upper gastrointestinal lesions.
- More studies are needed to evaluate the efficacy and strategy of cancers screening among high-risk individuals/groups in low and moderate-incidence regions/countries.
- More studies are needed to provide the best evidence-base recommendation on the surveillance intervals for gastric cancer precursor lesions, that is, atrophic gastritis and gastric intestinal metaplasia.

Trusted Websites for Further Reading

- National Cancer Institute Website:
https://www.cancer.gov/types/esophageal/hp
https://www.cancer.gov/types/stomach/hp
- Medscape Website:
https://emedicine.medscape.com/article/277930-overview
https://emedicine.medscape.com/article/278744-overview
- StatPearls (NCBI Bookshelf):
https://www.ncbi.nlm.nih.gov/books/NBK459267/
https://www.ncbi.nlm.nih.gov/books/NBK459142/
- MSD Manual (Professional version):
https://www.msdmanuals.com/professional/gastrointestinal-disorders/tumors-of-the-gastrointestinal-tract/esophageal-cancer
https://www.msdmanuals.com/professional/gastrointestinal-disorders/tumors-of-the-gastrointestinal-tract/stomach-cancer

References

Aalami, A.H., Abdeahad, H., and Mesgari, M. (2021). Circulating miR-21 as a potential biomarker in human digestive system carcinoma: a systematic review and diagnostic meta-analysis. *Biomarkers* 26 (2): 103–113. doi: 10.1080/1354750X.2021.1875504.

Abdallah, J., Maradey-Romero, C., Lewis, S. et al. (2015). The relationship between length of Barrett's esophagus mucosa and body mass index. *Aliment Pharmacol Ther* 41 (1): 137–144.

Abnet, C.C., Arnold, M., and Wei, W.Q. (2018). Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology* 154 (2): 360–373.

Abnet, C.C., Freedman, N.D., Hu, N. et al. (2010). A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nat Genet* 42 (9): 764–767.

Alexandre, L., Clark, A.B., Bhutta, H.Y. et al. (2016). Association between Statin use after diagnosis of Esophageal cancer and survival: a Population-based Cohort study. *Gastroenterology* 15: 854–865.e1.

Anderson, L.A., Cantwell, M.M., Watson, R.G.P. et al. (2009). The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. *Gastroenterology* 136 (3): 799–805.

Arai, J., Niikura, R., Hayakawa, Y. et al. (2021). Chemoprevention of Oesophageal Squamous-cell Carcinoma and Adenocarcinoma: a multicentre retrospective Cohort study. *Digestion* 103 (3): 192–204. doi: 10.1159/000520924.

Azuma, T., Ohtani, M., Yamazaki, Y. et al. (2004). Meta-analysis of the relationship between CagA seropositivity and gastric cancer. *Gastroenterology* 126: 1926–1927.

Baik, D., Sheng, J., Schlaffer, K. et al. (2017). Abdominal diameter index is a strong predictor of prevalent Barrett´s esophagus than BMI or waist-to-hip ratio. *Dis Esophagus* 30 (9): 1–6.

Banks, M., Graham, D., Jansen, M. et al. (2019). British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut* 68 (9): 1545–1575. doi: 10.1136/gutjnl-2018-318126.

Bansal, A., Lee, I.H., Hong, X. et al. (2011). Feasibility of microRNAs as biomarkers for Barrett's esophagus progression: a pilot cross- sectional, phase 2 biomarker study. *Am J Gastroenterol* 106: 1055–1063.

Barb, D., Williams, C.J., Neuwirth, A.K. et al. (2007). Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *Am J Clin Nutr* 86 (3): s858–866.

Bertuccio, P., Rosato, V., Andreano, A. et al. (2013). Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. *Ann Oncol* 24 (6): 1450–1458. doi: 10.1093/annonc/mdt108.

Bhandari, P. (2017). Acetic acid chromoendoscopy in the setting of Neoplastic Barrett Esophagus. *Gastroenterol Hepatol (N Y)* 13 (8): 508–510.

Bhardwaj, A., Hollenbeak, C.S., Pooran, N. et al. (2009). A meta-analysis of the diagnostic accuracy of esophageal capsule endoscopy for Barrett's esophagus in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 104: 1533–1539.

Bhat, S., Coleman, H.G., Yousef, F. et al. (2011). Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 103 (13): 1049-1057.

Blair, V.R., McLeod, M., Carneiro, F. et al. (2020). Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 21 (8): e386–e397. doi: 10.1016/S1470-2045(20)30219-9.

Brown, L.M. and Devesa, S.S. (2002). Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am* 11 (2): 235-256.

Bus, P., Kestens, C., Ten Kate, F.J.W. et al. (2016). Profiling of circulating microRNAs in patients with Barrett's esophagus and esophageal adenocarcinoma. *J Gastroenterol* 51: 560–570.

Calanzani, N., Druce, P.E., Snudden, C. et al. (2021). Identifying novel biomarkers ready for evaluation in low-prevalence populations for the early detection of upper gastrointestinal cancers: a systematic review. *Adv Ther* 38 (2): 793–834. doi: 10.1007/s12325-020-01571-z.

Camargo, M.C., Goto, Y., Zabaleta, J. et al. (2012). Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. *Cancer Epidemiol, Biomarkers Prev* 21: 20–38.

Castellsagué, X., Muñoz, N., De Stefani, E. et al. (1999). Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *Int J Cancer* 82 (5): 657-664.

Chaber-Ciopinska, A., Kiprian, D., Kawecki, A. et al. (2016). Surveillance of patients at high-risk of squamous cell esophageal cancer. *Best Pract Res Clin Gastroenterol* 30 (6): 893-900.

Chandar, A.K., Anamay Sharma, A., and Amitabh Chak, A. (2020). Novel screening alternatives for barrett Esophagus. *Gastroenterol Hepatol* 16 (5): 238–245.

Chen, R., Liu, Y., Song, G. et al. (2021). Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. *Gut* 70 (2): 251–260. doi: 10.1136/gutjnl-2019-320200.

Chen, T., Cheng, H., Chen, X. et al. (2015). Family history of esophageal cancer increases the risk of esophageal squamous cell carcinoma. *Sci Rep* 5: 16038.

Chen, X.Z., Schöttker, B., Castro, F.A. et al. (2016). Association of helicobacter pylori infection and chronic atrophic gastritis with risk of colonic, pancreatic and gastric cancer: a ten-year follow-up of the ESTHER cohort study. *Oncotarget* 7 (13): 17182–17193.

Cheng, C., Zhou, Y., Li, H. et al. (2016). Whole-genome sequencing reveals diverse models of structural variations in esophageal squamous cell carcinoma. *Am J Hum Genet* 98 (2): 256–274.

Chettouh, H., Mowforth, O., Galeano-Dalmau, N. et al. (2018). Methylation panel is a diagnostic biomarker for Barrett's oesophagus in endoscopic biopsies and non-endoscopic cytology specimens. *Gut* 67 (11): 1942–1949. doi: 10.1136/gutjnl-2017-314026.

Chiang, T.H., Chang, W.J., Chen, S.L.S. et al. (2021). Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. *Gut* 70 (2): 243–250. doi: 10.1136/gutjnl-2020-322200.

Cho, E., Kang, M.H., Choi, K.S. et al. (2013). Cost-effectiveness outcomes of the national gastric cancer screening program in South Korea. *Asian Pac J Cancer Prev* 14: 2533–2540.

Choi, K.S., Jun, J.K., Park, E.C. et al. (2012). Performance of different gastric cancer screening methods in Korea: a population-based study. *PLoS One* 7 (11): e50041. doi: 10.1371/journal.pone.0050041.

Chun, N. and Ford, J.M. (2012). Genetic testing by cancer site: stomach. *Cancer J* 18: 355–363.

Coletta, M., Sami, S.S., Nachiappan, A. et al. (2016). Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 83: 57–67.e1.

Cook, M.B., Chow, W.H., and Devesa, S.S. (2009). Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. *Br J Cancer* 101 (5): 855-859.

Cook, M.B., Kamangar, F., Whiteman, D.C. et al. (2010). Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst* 102 (17): 1344-1353.

Corley, D.A., Kerlikowske, K., Verma, R. et al. (2003). Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 124: 47–56.

Correa, P. (1992). Human gastric carcinogenesis: a multistep and multifactorial process. First American cancer society award lecture on cancer epidemiology and prevention. *Cancer Res* 52: 6735–6740.

Crafa, P., Russo, M., Miraglia, C. et al. (2018). From Sidney to OLGA: an overview of atrophic gastritis. *Acta Biomed* 89 (8-S): 93–99.

D'Elia, L., Rossi, G., Ippolito, R. et al. (2012). Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clinical Nutrition* 31 (4): 489–498. doi: 10.1016/j.clnu.2012.01.003.

Dal Maso, L., Augustin, L.S., Karalis, A. et al. (2004). Circulating adiponectin and endometrial cancer risk. *J Clin Endocrinol Metab* 89 (3): 1160–1163.

Daly, M.B., Pal, T., Berry, M.P. et al. (2021). Genetic/Familial High-Risk Assessment: breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Network* 19 (1): 77–102. doi: 10.6004/jnccn.2021.0001.

de Vries, A.C. and Kuipers, E.J. (2007). Epidemiology of premalignant gastric lesions: implications for the development of screening and surveillance strategies. *Helicobacter* 12 (suppl 2): 22–31.

de Vries, A.C., van Grieken, N.C., Looman, C.W. et al. (2008). Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 134: 945–952.

Derakhshan, M.H., Liptrot, S., Paul, J. et al. (2009). Oesophageal and gastric intestinal-type adenocarcinomas show the same male predominance due to a 17-year delayed development in females. *Gut* 58: 16–23.

Dong, J., Buas, M.F., Gharahkhani, P. et al. (2018). Determining risk of Barrett's esophagus and esophageal adenocarcinoma based on epidemiologic factors and genetic variants. *Gastroenterology* 154 (5): 1273-1281.

Duggan, C., Onstad, L., Hardikar, S. et al. (2013). Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 11 (8): 934–943.

Dulai, G.S., Guha, S., Kahn, K.L. et al. (2002). Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. *Gastroenterology* 122 (1): 26–33.

Dvorak, K., Chavarria, M., Payne, C.M. et al. (2007). Activation of the interleukin-6/STAT3 antiapoptotic pathway in esophageal cells by bile acids and low pH: relevance to Barrett's esophagus. *Clin Cancer Res* 13 (18): 5305–5313.

Edelstein, Z.R., Farrow, D.C., Bronner, M.P. et al. (2007). Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 133 (2): 403–411.

El-Serag, H.B., Graham, D.Y., Satia, J.A. et al. (2005). Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *Am J Gastroenterol* 100 (6): 1243–1250.

El-Serag, H.B., Naik, A.D., Duan, Z. et al. (2016). Surveillance endoscopy is associated with improved outcomes of oesophageal adenocarcinoma detected in patients with Barrett's oesophagus. *Gut* 65 (8): 1252–1260. doi: 10.1136/gutjnl-2014-308865.

Engel, L.S., Chow, W.H., Vaughan, T.L. et al. (2003). Population attributable risks of esophageal and gastric cancers. *Journal of National Cancer Institute* 95 (18): 1404–1413.

Falk, G.W., Chittajallu, R., Goldblum, J.R. et al. (1997). Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. *Gastroenterology* 112: 1787–1797.

Fan, X., Qin, X., Zhang, Y. et al. (2021). Screening for gastric cancer in China: advances, challenges and visions. *Chin J Cancer Res* 33 (2): 168–180. doi: 10.21147/j.issn.1000-9604.2021.02.05.

Fassan, M., Volinia, S., Palatini, J. et al. (2011). MicroRNA expression profiling in human Barrett's carcinogenesis. *Int J Cancer* 129: 1661–1670.

Felsenreich, D.M., Kefurt, R., Schermann, M. et al. (2017). Reflux, sleeve dilation, and Barrett's Esophagus after laparoscopic sleeve gastrectomy: long-term follow-up. *Obes Surg* 27 (12): 3092–3101.

Fernandez-Riejos, P., Najib, S., Santos-Alvarez, J. et al. (2010). Role of leptin in the activation of immune cells. *Mediators Inflamm* 2010 (1–8): 568343.

Fitzgerald, R.C., di Pietro, M., Ragunath, K. et al. (2014). British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 63: 7–42.

Fitzgerald, R.C., di Pietro, M., Rugunath, K. et al. (2013). British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 0: 1–36. doi: 1-.1136/gutjnl-2013-305372.

Fock, K.M., Talley, N., Goh, K.L. et al. (2016). Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. *Gut* 65: 1402–1415. doi: 10.1136/gutjnl-2016-311715.

Freedman, N.D., Park, Y., Subar, A.F. et al. (2007). Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer* 121 (12): 2753-2760.

Fuccio, L., Zagari, R.M., Eusebi, L.H. et al. (2009). Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 151 (2): 121–128. doi: 10.7326/0003-4819-151-2-200907210-00009.

Gammon, M.D., Terry, M.B., Arber, N. et al. (2004). Nonsteroidal anti-inflammatory drug use associated with reduced incidence of adenocarcinomas of the esophagus and gastric cardia that overexpress cyclin D1: a population-based study. *Cancer Epidemiol, Biomarkers Prev* 13: 34–39.

Gao, Y.B., Chen, Z.L., Li, J.G. et al. (2014). Genetic landscape of esophageal squamous cell carcinoma. *Nat Genet* 46 (10): 1097-1102.

Garidou, A., Tzonou, A., Lipworth, L. et al. (1996). Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. *Int J Cancer* 68 (3): 295-299.

Genco, A., Soricelli, E., Casella, G. et al. (2017). Gastroesophageal reflux disease and Barrett's esophagus after laparoscopic sleeve gastrectomy: a possible, underestimated long-term complication. *Surg Obes Relat Dis* 13 (4): 568–574.

González, C.A., Jakszyn, P., Pera, G. et al. (2006). Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 98 (5): 345–354. doi: 10.1093/jnci/djj071.

Gonzalez, C.A., Sanz-Anquela, J.M., Gisbert, J.P. et al. (2013). Utility of subtyping intestinal metaplasia as marker of gastric cancer risk. A review of the evidence. *Int J Cancer* 133: 1023–1032.

Grady, W.M., Yu, M., Markowitz, S.D. et al. (2020). Barrett's Esophagus and Esophageal Adenocarcinoma biomarkers. *Cancer Epidemiol, Biomarkers Prev* 29 (12): 2486–2494. doi: 10.1158/1055-9965.EPI-20-0223.

Gupta, S., Li, D., El Serag, H.B. et al. (2020). AGA clinical practice guidelines on management of gastric intestinal metaplasia. *Gastroenterology* 158 (3): 693–702. doi: 10.1053/j.gastro.2019.12.003.

Hamashima, C. (2014). Current issues and future perspectives of gastric cancer screening. *World J Gastroenterol* 20 (38): 13767-13774.

Hamashima, C. (2018). Update version of the Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 48 (7): 673-683.

Hamashima, C., Shabana, M., Okada, K. et al. (2015). Mortality reduction from gastric cancer by endoscopic and radiographic screening. *Cancer Sci* 106 (12): 1744-1749.

Hansford, S., Kaurah, P., Li-Chang, H. et al. (2015). Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol* 1: 23–32.

Heberle, C.R., Omidvari, A.H., Ali, A. et al. (2017). Cost effectiveness of screening patients with gastroesophageal reflux disease for Barrett's esophagus with a minimally invasive cell sampling device. *Clin Gastroenterol Hepatol* 15 (1397–1404): e7.

Helicobacter and Cancer Collaborative Group (2001). Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 49: 347–353.

Howard, J.M., Cathcart, M.C., Healy, L. et al. (2014). Leptin and adiponectin receptor expression in oesophageal cancer. *Br J Sur* 101 (6): 643–652.

Huang, J., Koulaouzidis, A., Marlicz, W. et al. (2021). Global burden, risk factors, and trends of Esophageal cancer: an analysis of cancer registries from 48 countries. *Cancers* 13 (1): 141. doi: 10.3390/cancers13010141.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (1994). Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum* 61: 1–241.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2012). Personal Habits and Indoor Combustions. Volume 100E. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 100 (PtE): 1–538.

Islami, F., Boffetta, P., Ren, J.S. et al. (2009a). High-temperature beverages and foods and esophageal cancer risk—a systematic review. *Int J Cancer* 125 (3): 491-524.

Islami, F., Ren, J.S., Taylor, P.R. et al. (2009b). Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. *Br J Cancer* 101 (9): 1641-1647.

Iyer, P.G., Taylor, W.R., Johnson, M.L. et al. (2018). Highly discriminant methylated DNA markers for the non-endoscopic detection of Barrett's esophagus. *Am J Gastroenterol* 113: 1156–1166.

Jain, K.S., Sikora, A.G., Baxi, S.S. et al. (2013). Synchronous cancers in patients with head and neck cancer: risks in the era of human papillomavirus-associated oropharyngeal cancer. *Cancer* 119 (10): 1832–1837. doi: 10.1002/cncr.27988.

Jankowski, J.A.Z., de Caestecker, J., Love, S.B. et al. (2018). Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. *Lancet* 392: 400–408.

Jobe, B.A., Hunter, J.G., Chang, E.Y. et al. (2006). Office- based unsedated small-caliber endoscopy is equivalent to conventional sedated endoscopy in screening and surveillance for Barrett's esophagus: a randomized and blinded comparison. *Am J Gastroenterol* 101: 2693–2703.

Jun, J.K., Choi, K.S., Lee, H.Y. et al. (2017). Effectiveness of the Korean National Cancer screening program in reducing gastric cancer mortality. *Gastroenterology* 152 (6): 1319–1328.e7. doi: 10.1053/j.gastro.2017.01.029.

Kadri, S.R., Lao-Sirieix, P., O'Donovan, M. et al. (2010). Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. *BMJ* 341: c4372.

Karimi, P., Islami, F., Anandasabapathy, S. et al. (2014). Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol, Biomarkers Prev* 23: 700–713.

Kastelein, F., van Olphen, S.H., Steyerberg, E.W. et al. (2016). Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. *Gut* 65 (4): 548-554.

Kato, S., Matsukura, N., Tsukada, K. et al. (2007). Helicobacter pylori infection-negative gastric cancer in Japanese hospital patients: incidence and pathological characteristics. *Cancer Sci* 98: 790–794.

Kikuchi, S., Wada, O., Nakajima, T. et al. (1995). Serum anti-Helicobacter pylori antibody and gastric carcinoma among young adults. Research group on prevention of gastric carcinoma among young adults. *Cancer* 75: 2789–2793.

Kim, G.H., Liang, P.S., Bang, S.J. et al. (2016). Screening and surveillance for gastric cancer in the United States: is it needed? *Gastrointest Endosc* 84 (1): 18–28. doi: 10.1016/j.gie.2016.02.028.

Kishikawa, H., Kimura, K., Takarabe, S. et al. (2015): Helicobacter pylori antibody titer and gastric cancer screening. *Dis Markers* 2015: 156719.

Kitahara, F., Kobayashi, K., Sato, T. et al. (1999). Accuracy of screening for gastric cancer using serum pepsinogen concentrations. *Gut* 44: 693–697.

Kohoutova, D., Banks, M., and Bures, J. (2021). Advanced in the Aetiology and endoscopic detection and management of early gastric cancer. *Cancers* 13 (24): 6242. doi: 10.3390/cancers13246242.

Krishnamoorthi, R., Singh, S., Ragunathan, K. et al. (2018). Factors associated with progression of Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 16: 1046–1055.

La Vecchia, C., Negri, E., Franceschi, S. et al. (1992). Family history and the risk of stomach and colorectal cancer. *Cancer* 70: 50–55.

Ladeiras-Lopes, R., Pereira, A.K., Nogueira, A. et al. (2008). Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control* 19 (7): 689–701.

Lagergren, J., Bergström, R., Lindgren, A. et al. (1999). Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *New Eng J Med* 340 (11): 825–831.

Lagergren, J., Bergström, R., Lindgren, A. et al. (2000). The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer* 85 (3): 340–346.

Lao-Sirieix, P. and Fitzgerald, R.C. (2012). Screening for oesophageal cancer. *Nat Rev Clin Oncol* 9: 278–287.

Larsson, S.C., Bergkvist, L., and Wolk, A. (2006). Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. *Cancer Epidemiol, Biomarkers Prev* 15: 1998–2001.

Lee, K.J., Inoue, M., Otani, T. et al. (2006). Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan. *Int J Cancer* 118 (9): 2315-2321.

Lee, S., Jun, J.K., Suh, M. et al. (2015). Gastric cancer screening uptake trends in Korea: results for the National cancer screening program from 2002 to 2011. *Medicine* 94 (8): e533.

Lee, Y.C., Chen, T.H., Chiu, H.M. et al. (2013). The benefit of mass eradication of Helicobacter pylori infection: a community-based study of gastric cancer prevention. *Gut* 62 (5): 676–682. doi: 10.1136/gutjnl-2012-302240.

Leeuwenburgh, I., Scholten, P., Alderliesten, J. et al. (2010). Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. *Am J Gastroenterol* 105 (10): 2144–2149.

Leidner, R.S., Ravi, L., Leahy, P. et al. (2012). The microRNAs, MiR-31 and MiR-375, as candidate markers in Barrett's esophageal carcinogenesis. *Genes Chromosomes Cancer* 51: 473–479.

Levine, D.M., Ek, W.E., Zhang, R. et al. (2013). A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. *Nat Genet* 45 (12): 1487–1493.

Levine, D.S., Haggitt, R.C., Blount, P.L. et al. (1993). An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* 105 (1): 40–50.

Li, S., Chung, D.C., and Mullen, J.T. (2019). Screening high-risk populations for esophageal and gastric cancer. *J Surg Oncol* 120 (5): 831–846. doi: 10.1002/jso.25656.

Liao, L.M., Vaughan, T.L., Corley, D.A. et al. (2012). Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. *Gastroenterology* 142 (3): 442–452.e5.

Lui, F.H., Tuan, B., Swenson, S.L. et al. (2014). Ethnic disparities in gastric cancer incidence and survival in the USA: an updated analysis of 1992-2009 SEER data. *Dig Dis Sci* 59 (12): 3027–3034. doi: 10.1007/s10620-014-3275-3.

Luzna, P., Gregar, J., Uberall, I. et al. (2011). Changes of microRNAs-192, 196a and 203 correlate with Barrett's esophagus diagnosis and its progression compared to normal healthy individuals. *Diagn Pathol* 6: 114.

Ma, J.L., Zhang, L., Brown, L.M. et al. (2012). Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 104 (6): 488–492. doi: 10.1093/jnci/djs003.

Maitra, I., Date, R.S., and Martin, F.L. (2020). Towards screening Barrett's oesophagus: current guidelines, imaging modalities and future developments. *Clin J Gastroenterol* 13 (5): 635–649. doi: 10.1007/s12328-020-01135-2.

Mandeville, Y., Van Looveren, R., Vancoillie, P.J. et al. (2017). Moderating the enthusiasm of sleeve gastrectomy: up to fifty percent of reflux symptoms ten years in a consecutive series of 100 laparoscopic sleeve gastrectomies. *Obes Sur* 27 (7): 1797–1803.

Mansour, N.M., Groth, S.S., and Anandasabapathy, S. (2017). Esophageal adenocarcinoma: screening, surveillance, and management. *Ann Rev Med* 68: 213–227.

Marger, R.S. and Marger, D. (1993). Carcinoma of the esophagus and tylosis. A lethal genetic combination. *Cancer* 72 (1): 17-19.

Maru, D.M., Singh, R.R., Hannah, C. et al. (2009). MicroRNA-196a is a potential marker of progression during Barrett's metaplasia-dysplasia-invasive adenocarcinoma sequence in esophagus. *Am J Pathol* 174: 1940–1948.

Mathus-Vliegen, E.M. and Tygat, G.N. (2002). Gastro-oesophageal reflux in obese subjects: influence of overweight, weight loss and chronic gastric balloon distension. *Scand J Gastroenterol* 37 (11): 1246–1252.

Mathus-Vliegen, L.M. and Tytgat, G.N. (1996). Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension. *Eur J Gastroenterol Hepatol* 8 (7): 635–640.

Matos, J.I., de Sousa, H.A., Marcos-Pinto, R. et al. (2013). Helicobacter pylori CagA and VacA genotypes and gastric phenotype: a meta-analysis. *Eur J Gastroenterol Hepatol* 25: 1431–1441.

Matsumoto, S. (2007). Results of mass endoscopic examination for gastric cancer in Kamigoto Hospital, Nagasaki Prefecture. *World J Gastroenterol* 13 (32): 4316-4320.

Meijssen, M.A., Tilanus, H.W., van Blankenstein, M. et al. (1992). Achalasia complicated by oesophageal squamous cell carcinoma: a prospective study in 195 patients. *Gut* 33: 155–158.

Mitchell, H.M., Li, Y.Y., Hu, P.J. et al. (1992). Epidemiology of Helicobacter pylori in southern China: identification of early childhood as the critical period for acquisition. *J Infect Dis* 166: 149–153.

Mizoue, T., Yoshimura, T., Tokui, N. et al. (2003). Prospective study of screening for stomach cancer in Japan. *Int J Cancer* 106 (1): 103-107.

Moinova, H.R., LaFramboise, T., Lutterbaugh, J.D. et al. (2018). Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. *Sci Transl Med* 10: eaao5848.

Monahan, K.J., Bradshaw, N., Dolwani, S. Hereditary CRC guidelines eDelphi consensus group et al. (2020). Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut* 69: 411–444.

Moriarty, J.P., Shah, N.D., Rubenstein, J.H. et al. (2018). Costs associated with Barrett's esophagus screening in the community: an economic analysis of a prospective randomized controlled trial of sedated versus hospital unsedated versus mobile community unsedated endoscopy. *Gastrointest Endosc* 87: 88–94.e2.

Ness-Jensen, E., Lindam, A., Lagergren, J. et al. (2013). Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: the HUNT study. *Am J Gastroenterol* 108 (3): 376–382.

Nguyen, T., Duan, Z., Naik, A.D. et al. (2015). Statin use reduces risk of esophageal adenocarcinoma in US veterans with Barrett's esophagus: a nested case-control study. *Gastroenterology* 149 (6): 1392–1398. doi: 10.1053/j.gastro.2015.07.009.

Nielsen, S.F., Nordestgaard, B.G., and Bojesen, S.E. (2012). Statin use and reduced cancer- related mortality. *New Engl J Med* 367: 1792–1802.

Palli, D., Galli, M., Caporaso, N.E. et al. (1994). Family history and risk of stomach cancer in Italy. *Cancer Epidemiol, Biomarkers Prev* 3: 15–18.

Pan, K.F., Zhang, L., Gerhard, M. et al. (2016). A large randomised controlled intervention trial to prevent gastric cancer by eradication of Helicobacter pylori in Linqu County, China: baseline results and factors affecting the eradication. *Gut* 65 (1): 9–18. doi: 10.1136/gutjnl-2015-309197.

Pan, R., Zhu, M., Yu, C. et al. (2017). Cancer incidence and mortality: a cohort study in China, 2008-2013. *Int J Cancer* 141 (7): 1315–1323.

Park, Y.H. and Kim, N. (2015). Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. *J Cancer Prev* 20: 25–40.

Pascarenco, O.D., Coroș, M.F., Pascarenco, G. et al. (2016). A preliminary feasibility study: narrow-band imaging targeted versus standard white light endoscopy non-targeted biopsies in a surveillance Barrett's population. *Dig Liver Dis* 48: 1048–1053.

Peery, A.F., Hoppo, T., Garman, K.S. et al. (2012). Feasibility, safety, acceptability, and yield of office-based, screening transnasal esophagoscopy (with video). *Gastrointest Endosc* 75: 945–953.e2.

Peterli, R., Wolnerhanssen, B.K., Peters, T. et al. (2018). Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-enY gastric bypass on weight loss in patients with morbid obesity: the SM-BOSS randomized clinical trial. *JAMA* 319 (3): 255–265.

Pilonis, N.D., Januszewicz, W., and di Pietro, M. (2022). Confocal laser endomicroscopy in gastro-intestinal endoscopy: technical aspects and clinical applications. *Transl Gastroenterol Hepatol* 7: 7. doi: 10.21037/tgh.2020.04.02.

Pilonis, N.D., Tischkowitz, M., Fitzgerald, R.C. et al. (2021). Hereditary diffuse gastric cancer: approaches to screening, surveillance, and treatment. *Ann Rev Med* 72: 263–280. doi: https://doi.org/10.1146/annurev-med-051019-103216.

Pimentel-Nunes, P., Libânio, D., and Marcos-Pinto, R. (2019). Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy* 51 (4): 365–388. doi: 10.1055/a-0859-1883.

Pohl, H., Pech, O., Arash, H. et al. (2016). Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma. *Gut* 65 (2): 196–201. doi: 10.1136/gutjnl-2015-309220.

Qumseya, B.J., Bukannan, A., Gendy, S. et al. (2019). Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. *Gastrointest Endosc* 90: 707–717.

Rawla, P. and Barsouk, A. (2019). Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol* 14 (1): 26–38. doi: 10.5114/pg.2018.80001.

Redston, M., Noffsinger, A., Kim, A. et al. (2022). Abnormal TP53 predicts risk of progression in patients with Barrett's Esophagus regardless of a diagnosis of dysplasia. *Gastroenterology* 162 (2): 468–481. doi: 10.1053/j.gastro.2021.10.038.

Revilla-Nuin, B., Parrilla, P., Lozano, J.J. et al. (2013). Predictive value of microRNAs in the progression of Barrett esophagus to adenocarcinoma in a long-term follow-up study. *Ann Surg* 257: 886–893.

Riboli, E. and Norat, T. (2003). Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr* 78: 559S–569S.

Roberts, M.E., Ranola, J.M.O., Marshall, M.L. et al. (2019). Comparison of CDH1 penetrance estimates in clinically ascertained families versus families ascertained for multiple gastric cancers. *JAMA Oncol* 5 (9): 1325–1331.

Ross-Innes, C.S., Debiram-Beecham, I., O'Donovan, M. et al. (2015). Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multicenter case–control study. *PLoS Med* 12: e1001780.

Rubenstein, J.H., Mattek, N., and Eisen, G. (2010a). Age- and sex-specific yield of Barrett's esophagus by endoscopy indication. *Gastrointest Endosc* 71 (1): 21–27. doi: 10.1016/j.gie.2009.06.035.

Rubenstein, J.H., Morgenstern, H., Mcconell, D. et al. (2013). Associations of diabetes mellitus, insulin, leptin and ghrelin with gastroesophageal reflux and Barrett's esophagus. *Gastroenterology* 145 (6): 1237–1244.

Rubenstein, J.H. and Taylor, J.B. (2010b). Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Ther* 32 (10): 1222–1227.

Salehi, M., Moradi-Lakeh, M., Salehi, M.H. et al. (2013). Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. *Nutr Rev* 71 (5): 257-267.

Salminen, P., Helmio, M., Ovaska, J. et al. (2018). Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS randomized clinical trial. *JAMA* 319 (3): 241–254.

Sanghi, V. and Thota, P.N. (2019). Barrett's esophagus: novel strategies for screening and surveillance. *Ther Adv Chronic Dis* 26: 10. 2040622319837851 doi: 10.1177/2040622319837851.

Sato, F., Jin, Z., Schulmann, K. et al. (2008). Three-tiered risk stratification model to predict progression in Barrett's esophagus using epigenetic and clinical features. *PLoS ONE* 3 (4): e1890. doi: 10.1371/journal.pone.0001890.

Schlottmann, F., Dreifuss, N.H., and Patti, M.G. (2020). Obesity and esophageal cancer: GERD, Barrett´s esophagus, and molecular carcinogenic pathways. *Expert Rev Gastroenterol Hepatol* 14 (6): 425–433. doi: 10.1080/17474124.2020.1764348.

Schoofs, N., Bisschops, R., and Prenen, H. (2017). Progression of Barrett's esophagus toward esophageal adenocarcinoma: an overview. *Ann Gastroenterol* 30 (1): 1–6.

Schulmann, K., Sterian, A., Berki, A. et al. (2005). Inactivation of p16, RUNX3, and HPP1 occurs early in Barrett's-associated neoplastic progression and predicts progression risk. *Oncogene* 24: 4138–4148.

Sekiguchi, M., Oda, I., Matsuda, T. et al. (2021). Epidemiological trends and future perspectives of gastric cancer in Eastern Asia. *Digestion* 1: 1–7. doi: 10.1159/000518483.

Shah, S.C., Piazuelo, M.B., Kuipers, E.J. et al. (2021). AGA clinical practice update on the diagnosis and management of Atrophic Gastritis: expert review. *Gastroenterology* 161 (4): 1325–1332.e7. doi: 10.1053/j.gastro.2021.06.078.

Shah, T., Lippman, R., Kohli, D. et al. (2018). Accuracy of probe-based confocal laser endomicroscopy (pCLE) compared to random biopsies during endoscopic surveillance of Barrett's esophagus. *Endosc Int Open* 06: E414–E420.

Shaheen, N.J., Falk, G.W., Iyer, P.G. et al. (2016). ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol* 111 (1): 30–50.

Shaheen, N.J., Falk, G.W., Iyer, P.G. et al. (2022). Diagnosis and management of Barrett's Esophagus: An updated ACG guideline. *Am J Gastroenterol* 117: 559–587.

Shapiro, J., van Lanschot, J.J.B., Hulshof, M. et al. (2015). Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 16: 1090–1098. doi: 10.1016/S1470-2045(15)00040-6.

Shariff, M.K., Bird-Lieberman, E.L., O'Donovan, M. et al. (2012). Randomized crossover study comparing efficacy of transnasal endoscopy with that of standard endoscopy to detect Barrett's esophagus. *Gastrointest Endosc* 75: 954–961.

Sheh, A., Ge, Z., Parry, N.M. et al. (2011). 17Beta-estradiol and tamoxifen prevent gastric cancer by modulating leukocyte recruitment and oncogenic pathways in Helicobacter pylori-infected INS-GAS male mice. *Cancer Prev Res (Phila)* 4: 1426–1435.

Shikata, K., Kiyohara, Y., Kubo, M. et al. (2006). A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer* 119 (1): 196–201. doi: 10.1002/ijc.21822.

Shin, C.M., Kim, N., Yang, H.J. et al. (2010). Stomach cancer risk in gastric cancer relatives: interaction between Helicobacter pylori infection and family history of gastric cancer for the risk of stomach cancer. *J Clin Gastroenterol* 44: e34–39.

Singh, S., Garg, S.K., Singh, P.P. et al. (2014a). Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut* 63 (8): 1229–12237. doi: 10.1136/gutjnl-2013-305997.

Singh, S., Manickam, P., Amin, A.V. et al. (2014b). Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 79: 897–909.

Singh, S., Sharma, A.N., Murad, M.H. et al. (2013a). Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 11 (11): 1399–1412.

Singh, S., Singh, A.G., Singh, P.P. et al. (2013b). Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 11 (6): 620–629. doi: 10.1016/j.cgh.2012.12.036.

Smith, C.M., Watson, D.I., Leong, M.P. et al. (2011). miR-200 family expression is downregulated upon neoplastic progression of Barrett's esophagus. *World J Gastroenterol* 17: 1036–1044.

Stein, D.J., El-Serag, H.B., Kuczynski, J. et al. (2005). The association of body mass index with Barrett's esophagus. *Aliment Pharmacol Ther* 22 (10): 1005–1010.

Su, Z., Gay, L.J., Strange, A. et al. (2012). Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. *Nat Genet* 44 (10): 1131–1136.

Sugano, K. (2015). Screening of gastric cancer in Asia. *Best Pract Res Clin Gastroenterol* 29 (6): 895–905.

Sung, H., Ferlay, J., Siegel, R.L. et al. (2021). Global cancer statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin* 71 (3): 209–249. doi: 10.3322/caac.21660.

Sutton, P. and Boag, J.M. (2019). Status of vaccine research and development for Helicobacter pylori. *Vaccine* 37 (50): 7295–7299. doi: 10.1016/j.vaccine.2018.01.001.

Tashiro, A., Sano, M., Kinameri, K. et al. (2006). Comparing mass screening techniques for gastric cancer in Japan. *World J Gastroenterol* 12 (30): 4873-4874.

Thosani, N., Abu Dayyeh, B.K., Sharma, P. et al. (2016). ASGE technology committee systematic review and meta-analysis assessing the ASGE preservation and incorporation of valuable endoscopic innovations thresholds for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance. *Gastrointest Endosc* 83: 684–698.e7.

Thota, P.N., Zuccaro, G., Jr, Vargo, J.J., II et al. (2005). A randomized prospective trial comparing unsedated esophagoscopy via transnasal and transoral routes using a 4-mm video endoscope with conventional endoscopy with sedation. *Endoscopy* 37: 559–565.

Tramacere, I., Negri, E., Pelucchi, C. et al. (2012). A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol* 23 (1): 28-36.

Tselepis, C., Perry, I., Dawson, C. et al. (2002). Tumour necrosis factor-alpha in Barrett's oesophagus: a potential novel mechanism of action. *Oncogene* 21: 6071–6081.

Tsugane, S. (2005). Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Sci* 96: 1–6.

Tworoger, S.S., Eliassen, A.H., Kelesidis, T. et al. (2007). Plasma adiponectin concentrations and risk of incident breast cancer. *J Clin Endocrinol Metabol* 92 (4): 1510–1516.

Uemura, N., Okamoto, S., Yamamoto, S. et al. (2001). Helicobacter pylori infection and the development of gastric cancer. *New Engl J Med* 345 (11): 784–789. doi: 10.1056/NEJMoa001999.

van der Post, R.S., Vogelaar, I.P., Carneiro, F. et al. (2015). Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet* 52 (6): 361-374.

van Leerdam, M.E., Roos, V.H., van Hooft, J.E. et al. (2019). Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: european Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 51 (11): 1082–1093. doi: 10.1055/a-1016-4977.

Wang, G.Q., Jiao, G.G., Chang, F.B. et al. (2004). Long- term results of operation for 420 patients with early squamous cell esophageal carcinoma discovered by screening. *Ann Thorac Surg* 77: 1740–1744.

Wang, L.D., Zhou, F.Y., Li, X.M. et al. (2010). Genome-wide association study of esophageal squamous cell carcinoma in Chinese subjects identifies a susceptibility locus at PLCE1. *Nat Genet* 42 (9): 759-763.

Wang, Q.L., Xie, S.H., Li, W.T. et al. (2017). Smoking cessation and risk of esophageal cancer by histological type: systematic review and meta-analysis. *J Natl Cancer Inst* 109 (12).doi:10.1093/jnci/djx115.

Wei, E.K., Giovannucci, E., Fuchs, C.S. et al. (2005). Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. *J Natl Cancer Inst* 97 (22): 1688–1694.

Wei, W.Q., Chen, Z.F., He, Y.T. et al. (2015). Long-Term follow-up of a community assignment, one-time endoscopic screening study of esophageal cancer in China. *J Clin Oncol* 33: 1951–1957.

Wong, B.C., Lam, S.K., Wong, W.M. et al. (2004). Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 291 (2): 187–194. doi: 10.1001/jama.291.2.187.

Wong, M.C.S., Huang, J., Wang, J. et al. (2020). Global, regional and time-trend prevalence of central obesity: a systematic review and meta-analysis of 13.2 million subjects. *Eur J Epidemiol* 35: 673–683. doi: 10.1007/s10654-020-00650-3.

Wu, A.H., Tseng, C.C., and Bernstein, L. (2003). Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 98: 940–948.

Yaghoobi, M., Bijarchi, R., and Narod, S.A. (2010). Family history and the risk of gastric cancer. *Br J Cancer* 102: 237–242.

Yamaguchi, Y., Nagata, Y., Hiratsuka, R. et al. (2016). Gastric cancer screening by combined assay for serum anti-*Helicobacter pylori* IgG antibody and serum pepsinogen levels – the ABC method. *Digestion* 93: 13–18. doi: 10.1159/000441742.

Yang, J., Wei, W.Q., Niu, J. et al. (2012). Cost-benefit analysis of esophageal cancer endoscopic screening in high-risk areas of China. *World J Gastroenterol* 18: 2493–2501.

Yang, P., Zhou, Y., Chen, B. et al. (2009). Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer* 45 (16): 2867–2873. doi: 10.1016/j.ejca.2009.04.019.

Yeung, K.T.D., Penney, N., Ashrafian, L. et al. (2020). Does sleeve gastrectomy expose the distal esophagus to severe reflux?: a systematic review and meta-analysis. *Ann Sur* 271 (2): 257–265.

Yoon, H. and Kim, N. (2015). Diagnosis and management of high risk group for gastric cancer. *Gut Liver* 9 (1): 5–17. doi: 10.5009/gnl14118.

You, W.C., Blot, W.J., Chang, Y.S. et al. (1988). Diet and high risk of stomach cancer in Shandong, China. *Cancer Res* 48: 3518–3523.

Zakko, L., Lutzke, L., and Wang, K.K. (2017). Screening and Preventive Strategies in Esophagogastric Cancer. *Sur Oncol Clin North Am* 26 (2): 163–178. doi: 10.1016/j.soc.2016.10.004.

Zeng, H., Sun, K., Cao, M. et al. (2020). Initial results from a multi-center population-based cluster randomized trial of esophageal and gastric cancer screening in China. *BMC Gastroenterol* 20 (1): 398. doi: 10.1186/s12876-020-01517-3.

Zhang, X., Li, M., Chen, S. et al. (2018). Endoscopic screening in Asian countries is associated with reduced gastric cancer mortality: a meta-analysis and systematic review. *Gastroenterology* 155 (2): 347–354.e9. doi: 10.1053/j.gastro.2018.04.026.

4 Management of Esophageal Dysplasia and Esophageal Adenocarcinoma

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[Aspects of the management of esophageal squamous cancer, especially surgery are also covered in Chapter 5].
[Aspects of relevant colorectal date are covered in Chapter 11].

Epidemiology

Esophageal cancer is the seventh most common incident cancer, and is the sixth most common cause of mortality worldwide, disproportionately affecting men (Sung et al. 2021). In the United States alone, it is estimated that in 2022 there will be over 20,000 new cases of esophageal cancer resulting in over 16,000 deaths (Siegel et al. 2022).

Esophageal cancer has two major histologic subtypes: squamous cell carcinoma (ESCC), which is prevalent in East Asia, Central Asia, and Sub-Saharan Africa, and adenocarcinoma (EAC), which is found mainly in North America, Western Europe, and Australia (Arnold et al. 2020). EAC is more prevalent among those of Caucasian race (Then et al. 2020). EAC primarily affects males in the sixth or seventh decade of life. Furthermore, the incidence of EAC has increased over time beginning in the 1970s (Codipilly et al. 2021).

Barrett's esophagus (BE) is the single most important risk factor for EAC, and the risk of EAC increases depending on the degree of dysplasia within BE, ranging from 3.3/1,000 person years for those with non-dysplastic BE to 8/100 person years in those with high grade dysplasia (HGD) (Shaheen et al. 2016). The main risk factors for BE include male gender, age over 50 years, central obesity (waist circumference >102 cm or waist to hip ratio >0.9), current or past history of smoking, and family history of BE and/or EAC in a first-degree relative.

Pathological Features

Barrett esophagus is characterized by the normal squamous epithelium replaced by metaplastic columnar epithelium including goblet cell, paneth cells, and gastric foveolar cells and glands (both cardiac and oxyntic types) corresponding to the region of salmon colored appearance identified endoscopically in esophagus (Figure 1). In the United States, identification of intestinal metaplasia (goblet cells) is required for the histological diagnosis of Barrett esophagus (Shaheen NJ, Am J Gastroenterology 2016) based on the evidence only metaplastic columnar epithelium with presence of intestinal metaplasia is with increased risk of neoplastic progression. This presence of intestinal metaplasia is not required in Europe, only the histologically confirmed metaplastic columnar epithelium endoscopically visibly above the GEJ is sufficient for diagnosis of Barrett esophagus by British Society of Gastroenterology (Bennett C et al 2012, 2015). In fact, intestinal metaplasia can occur in the stomach whereas deep oesophageal gland ducts with metaplasia above and the mosaic of metaplasias only seen in Barrett's are diagnostic. Multilayered epithelium contains columnar epithelium with acidic mucin lying on top of a layer of stratified squamous cells and is thought to possibly representing a precursor or intermediate step in the development of Barrett esophagus (Glickman JN, AJSP 2001). It is often identified at the squamocolumnar junction in patients with gastroesophageal reflux of Barrett esophagus, the identification of multilayered epithelium of alone is not sufficient for diagnosis of Barrett esophagus.

Duplication of muscularis mucosae and fibromuscular anomaly with prolapse-type change can be seen in Barrett esophagus. Duplicated muscularis mucosae can be patchy or

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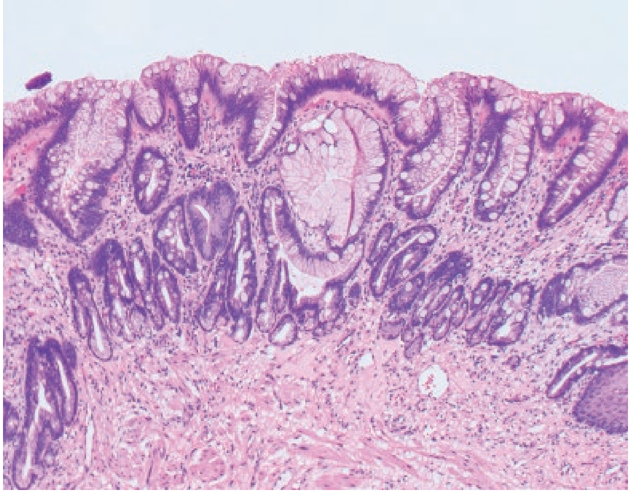

Figure 1 Histological feature of Barrett mucosa. In Barrett esophagus, the esophageal squamous epithelium is replaced by metaplastic columnar epithelium with Goblet cells in background of chronic inflammation in the lamina propria. The non-dysplastic Barrett mucosa shows basally located small nuclei without cytological atypia.

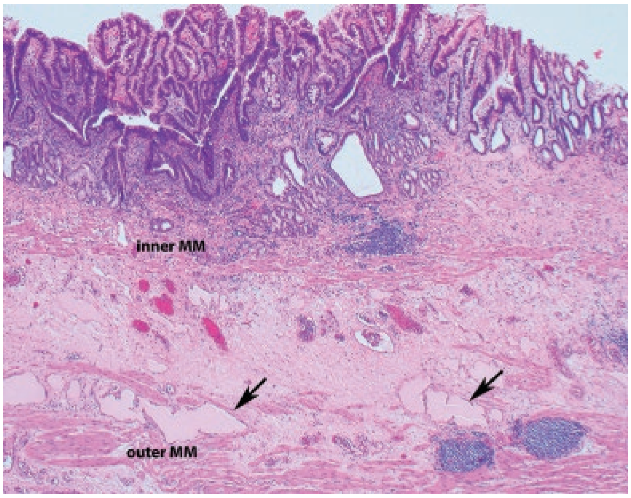

Figure 2 Duplicated muscularis mucosae in Barrett esophagus. The inner muscularis mucosae (inner MM) is the duplicated layer, and the outer muscularis mucosae (outer MM) is the layer continuous with the single layer of muscularis mucosae underlying the normal esophageal squamous mucosa. The space between inner and outer muscularis mucosae is loose fibroconnective rich with lymphatic vessels (arrows).

diffuse and is identified in up to 92% of Barrett esophagus in esophagectomy specimen (Abraham SC, AJSP 2007) and in 2/3 of EMR specimens (Prasad GA, AJG 2007) (Figure 2). The space between the duplicated muscularis mucosae contains loose connective tissue rich in lymphatics and medium sized vessels. Awareness of the presence of duplicated muscularis mucosae is important to avoid overstaging invasive Barrett adenocarcinoma in particularly in specimens from endoscopic therapy (EMR or ESD).

Dysplasia in Barrett Esophagus

Barrett esophagus is a preneoplastic condition, and it follows the scheme of progression through the metaplasia, dysplasia and adenocarcinoma. Therefore, it is important to evaluate for the presence of dysplasia during endoscopic surveillance biopsies and each Barrett mucosa biopsy will be classified as negative for dysplasia, indefinite for dysplasia, low grade dysplasia, high grade dysplasia or adenocarcinoma based on the characteristic histological features including cytology of the cells, glandular architecture, surface maturation, and presence of inflammation (Montgomery E, Human Pathol 2001).

- Negative for dysplasia: The Barrett epithelium shows no cytological atypia with typical small basally located nuclei, and the glands are even spaced without crowding or architectural complexity.
- Indefinite for dysplasia: This classification is used when the Barrett epithelium demonstrates epithelial atypia but does not reach the degree of low grade dysplasia or cannot be determined whether the changes are truly dysplastic or reactive in the presence of acute inflammation or tissue artifacts.
- Low grade dysplasia: The dysplastic epithelium shows mild nuclear hyperchromatism, mildly increased nuclear:cytoplasmic ratios with nuclear stratification, typically involves both deeper glands and surface epithelium. The nuclear polarity and glandular architecture are generally preserved with only mild crowding or distortion (Figure 3).
- High grade dysplasia: The dysplastic epithelium demonstrates more pronounced cytological atypia with enlarged nuclei and increased nuclear:cytoplasmic ratios, nuclear stratification involving full thickness of the cells and loss of nuclear polarity (Figure 4). Glandular architecture is more distorted than low grade dysplasia with marked crowding

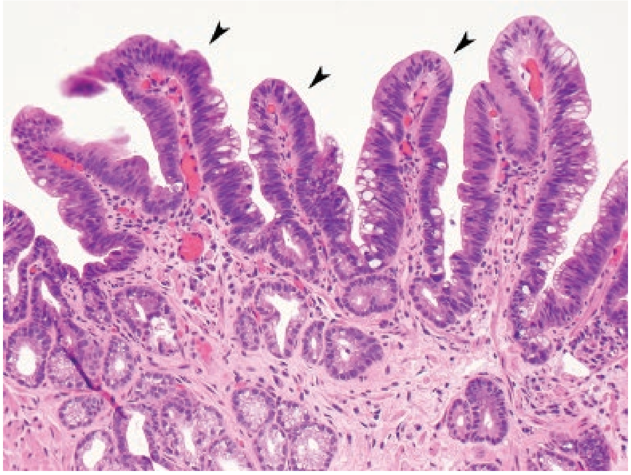

Figure 3 Barrett mucosa with low grade dysplasia. The dysplastic columnar epithelium (arrowheads) shows nuclear stratification and nuclear hyperchromatism involving surface and crypts. No loss of nuclear polarity is identified.

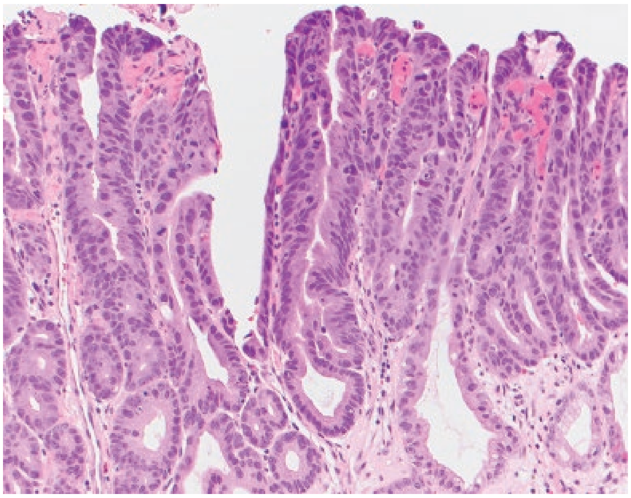

Figure 4 Barrett mucosa with high grade dysplasia. The dysplastic columnar epithelium shows marked cytological atypia with increased nuclear:cytoplasmic ratio, nuclear hyperchromatism and loss of nuclear polarity.

and glandular distortion. High grade dysplasia also typically involves both the deeper glands and surface epithelium and can present with cribriform architecture with intact basement membrane. Intraluminal necrotic debris present in the high grade dysplastic glands usually represent a sign of synchronous intramucosal or invasive adenocarcinoma (Odez RD, J Clin Pathol 2006). Endoscopic therapy is recommended for patients with Barrett esophagus with high grade dysplasia (Shaheen NJ 2016).

There are two main histological types of Barrett dysplasia, adenomatous (intestinal) type and non-adenomatous (foveolar) type. The adenomatous type dysplasia has histological features of prominent nuclear stratification with elongated pencil-shaped nuclei resembling colonic adenoma, is the most common type of dysplasia in Barrett esophagus. Non-adenomatous (foveolar) type dysplasia represents the dysplasia of the gastric foveolar component of the Barrett esophagus (Brown IS, Mod Pathol 2010, Mahajan D, Mod Pathol 2010) and accounts 6–8% of dysplastic Barrett esophagus in biopsy materials (Naini BV, AJSP 2016). Foveolar type dysplasia is characterized by glands with uniform round-oval, basally located, non-stratified nuclei and abundant pale eosinophilic cytoplasm typically involves the full thickness of mucosa. Low grade foveolar type dysplasia has uncrowded glands with preserved glandular architecture and enlarged nuclei of 2–3 times of mature lymphocyte. High grade foveolar dysplasia shows presence of back-to back crowded glands with glandular branching, complexity and occasional villiform pattern; and enlarged nuclei of 3–4 times the size of mature lymphocyte. Loss of nuclear polarity, a feature typically only present in high grade adenomatous type dysplasia can be present in both low grade and high grade foveolar type dysplasia.

Serrated type dysplasia is a rare form of Barrett dysplasia (Naini BV, AJSP 2016). Serrated dysplasia in Barrett esophagus shares similar histological features seen in colonic serrated adenoma. Dysplasia in Barrett esophagus has been described limited to the crypts without surface involvement as “crypt dysplasia” based on the nuclear and cytological features with clonal appearance distinctive from the adjacent non-dysplastic crypts (Lomo LC, AJSP 2006). The concept of crypt dysplasia is not universally accepted among gastrointestinal pathologists and some gastrointestinal pathologists prefer to use indefinite for dysplasia in this setting.

Dysplastic Barrett esophagus has increased risk of developing adenocarcinoma. The rate of developing adenocarcinoma in Barrett esophagus negative for dysplasia is 0.1–0.5%/year (Hvid-Jensen F, NEJM 2011). The rate of developing high grade dysplasia/adenocarcinoma for Barrett esophagus with indefinite for dysplasia is 0.86–1.4%/year, and with low grade dysplasia is 1.7–1.8%/year (Singh S, Gastrointestinal endoscopy. 2014). Barrett esophagus with high grade dysplasia has annual rate of 5–8% of developing adenocarcinoma .

Although histological features are the gold-standard for the diagnosis for dysplasia for Barrett esophagus and the clinical follow-ups are based on the absence or presence of dysplasia. There is considerable intraobserver and interobserver variations even among gastrointestinal pathologists in grading of Barrett dysplasia. There is a reasonable interobserver agreement in the categories of negative for dysplasia and high grade dysplasia; but significant discordance in the categories of indefinite for dysplasia and low grade dysplasia (Kerhof M, Histopathology 2007, Montgomery E, Human Pathol 2001). Diagnosis of dysplasia needs to be confirmed by a second pathologist with extensive experience in interpretation of Barrett-associated dysplasia as recommended by AGA clinical guideline (Shaheen NJ, Am J Gastroenterol 2016).

Adenocarcinoma

Adenocarcinoma is characterized by neoplastic epithelium that invades through the basement membrane into the surrounding stroma (Figure 5). Adenocarcinoma can show different degree of differentiation based on the extent of glandular formation as well-differentiated, moderately differentiated and poorly differentiated. There are different types of adenocarcinoma based on the histological pattern, intestinal type adenocarcinoma, mucinous adenocarcinoma, and signet ring cell type adenocarcinoma. The esophageal adenocarcinoma can be subclassified based on the depth of invasion as intramucosal adenocarcinoma (invading into lamina propria or muscularis mucosa) or invasive adenocarcinoma (invading into submucosa, muscularis propria or subserosa).

Intramucosal adenocarcinoma can be further subclassified into four levels based on the level of invasion as invading into lamina propria (m1), inner/superficial muscularis mucosae

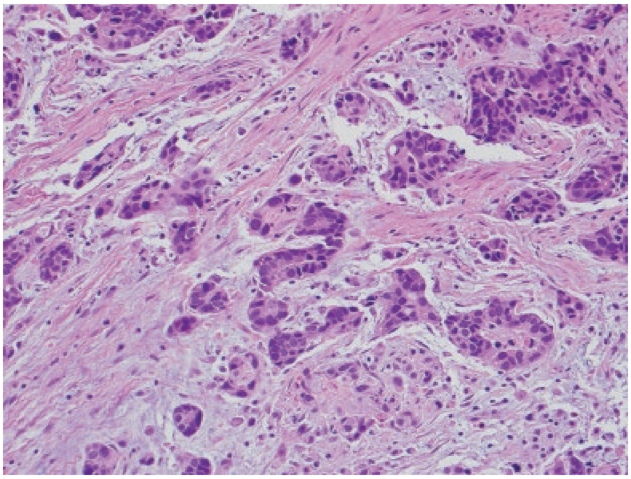

Figure 5 Barrett adenocarcinoma. A moderately to poorly differentiated adenocarcinoma showing neoplastic cells with focal glandular pattern invading into stroma.

(m2), space between the duplicated muscularis mucosae (m3) and outer/deep-muscularis mucosae (m4) by Vieth and Stolte system (Vieth M, Best Pr Res Clin Gastroentero 2005). Esophageal adenocarcinoma with submucosa invasion can be further subclassified as three levels based on the level of invasion as into superficial 1/3 of submucosa (sm1), middle 1/3 of submucosa (sm2) and outer 1/3 of submucosa (sm3). This subclassification requires the presence of entire thickness of submucosa and use muscularis propria as landmark, is difficult and inaccurate to use for endoscopic resection specimens typically containing variable thickness of submucosa and lacking muscularis propria as landmark. The Paris endoscopic classification of superficial neoplasms have recommended measuring depth of submucosa invasion in microns from the lower limit of muscularis mucosae on endoscopic resection specimens (Figure 6) (Endoscopic Classification Review Group, Endoscopy 2005).

Lymphovascular invasion can be identified in 0% to 12% of intramucosal adenocarcinoma and 22% to 60% of submucosal adenocarcinoma (Figure 7) (Estrella JS, AJSP 2011; Badreddine RJ, Clin Gastro & Hepato 2010). Tumor budding is present in 4% of intramucosal adenocarcinoma and 41% of submucosal adenocarcinoma; and tumor budding is more frequently present in adenocarcinomas with metastatic lymph node (41%) than in adenocarcinomas without metastatic lymph node (10%) (Landau MS, Mod Pathol 2014). Lymphovascular invasion and tumor budding are predictors for lymph node metastasis (Estrella JS, AJSP 2011; Landau MS, Mod Pathol 2014).

Esophageal intramucosal adenocarcinoma has minimal risk of lymph node metastasis (2%) and endoscopic therapy is preferred over esophagectomy for Barrett patients with intramucosal adenocarcinoma (Dunbar KB, AJG 2012). Esophageal submucosa adenocarcinoma has a higher risk (ranging from 18% to 33%) of lymph node involvement on esophagectomy specimens (Estrella JS, AJSP 2011; Badreddine RJ, Clin Gastro & Hepato 2010). The studies from esophagectomy specimens had shown no significant different rates of lymph node metastasis between superficial (sm1) and deeper (sm2 and sm3) submucosa adenocarcinoma (Badreddine RJ, Clin Gastro & Hepato 2010; Leers JM, Annals Surgery 2011;) and esophagectomy is the therapy choice for submucosal adenocarcinoma. However, with the widely accepted practice of endoscopic therapy, it has been shown that a subset of “low-risk” submucosal invasive adenocarcinoma defined as superficial submucosal invasion (<500 μm), absence of

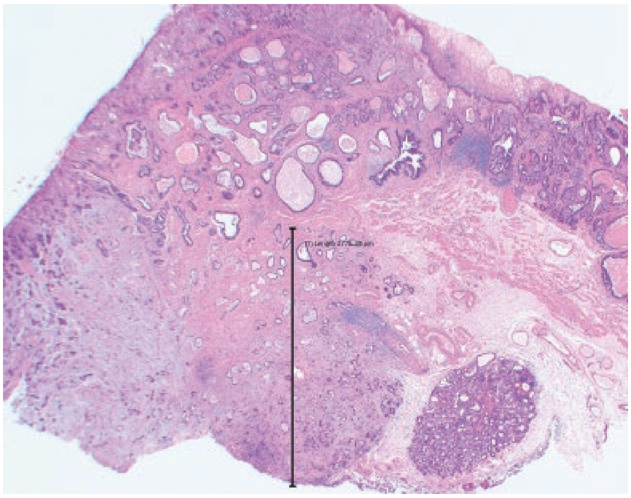

Figure 6 Submucosal adenocarcinoma. A low power view of adenocarcinoma invades into deep submucosa (sm3) with 2778 μm invasion into submucosa based on the measurement on an endoscopic mucosa resection specimen.

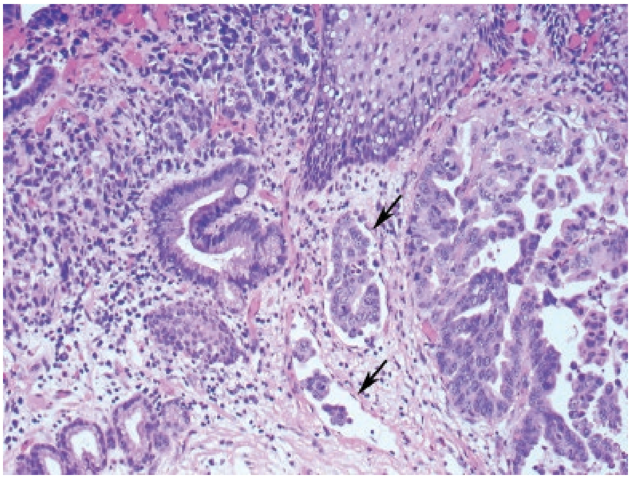

Figure 7 Barrett adenocarcinoma with lymphovascular invasion. Clusters of adenocarcinoma cells are present with the lymphatic vessels (arrows).

lymphovascular invasion, and histological grade G1/G2 (Manner H, AJG 2008); can be managed by endoscopic therapy especially in those who are poor surgical candidate as recommended by AGA Clinical Practice. The “low-risk” submucosal invasive adenocarcinoma has minimal (2%) risk of lymph node involvement or distant metastasis (Manner H, AJG 2008).

Pathophysiology

Barrett’s esophagus was original conceptualized by Norman Barrett as a congenital condition where gastric type epithelium was found in the distal esophagus. Even at its initial description, it was felt to be related to acid peptic disease with ulcer formation being the clinical significance of the disorder.

BE currently is felt to be the consequence of long-term gastroesophageal reflux disease producing chronic inflammation and subsequent immune cell infiltration that appears to be characteristic of metaplasia formation{(Fitzgerald et al. 2014) #7394}. There does appear to be a dependence on bile as well as acid reflux to induce metaplastic features in cell culture models of Barrett’s esophagus

Genomic abnormalities have been studied for decades in hopes of identifying potential biomarkers for progression of the disease to cancer. The two most significant tumor suppressor genes mutated in EAC are TP53 and p16/CDKN2A, though sporadic mutations have also been identified in various other genes including APC, BRAF, CDH1, CTNNB1, EGFR, KRAS, PIK3CA, PTEN, and SMAD4 (Dulak et al. 2013).

Molecular studies suggest that BE can progress to EAC in either a genome-doubled pathway or a non-genome-doubled pathway (Figure 8). In the genome-doubled pathway, TP53 inactivation occurs early, followed by genome doubling resulting in genomic instability, aneuploidy, and oncogene amplification. In the non-genome-doubled pathway, there is a gradual accumulation of mutations affecting tumor suppressor genes leading to activation of oncogenes and the subsequent development of genomic instability (Stachler et al. 2015).

The cancer genome atlas found that the predominant mechanism of genomic evolution in adenocarcinoma is related to genomic instability with multiple genetic pathways variable involved (Sanchez-Vega et al. 2018 #57743). Unfortunately, no distinct or predominant mechanism has been found. It is clear that p53 mutations occur late in the development of neoplasia while p16 inactivation through mutation, promoter hypermethylation, deletion, or recombination appears to occur much earlier.

Disease Presentation and Work-up

BE is typically asymptomatic though patients may present with a long duration of gastroesophageal reflux symptoms. Similarly, early stage EAC is frequently asymptomatic, but more advanced stage disease may present with dysphagia, odynophagia, hematemesis, weight loss, and/or fevers. Patients

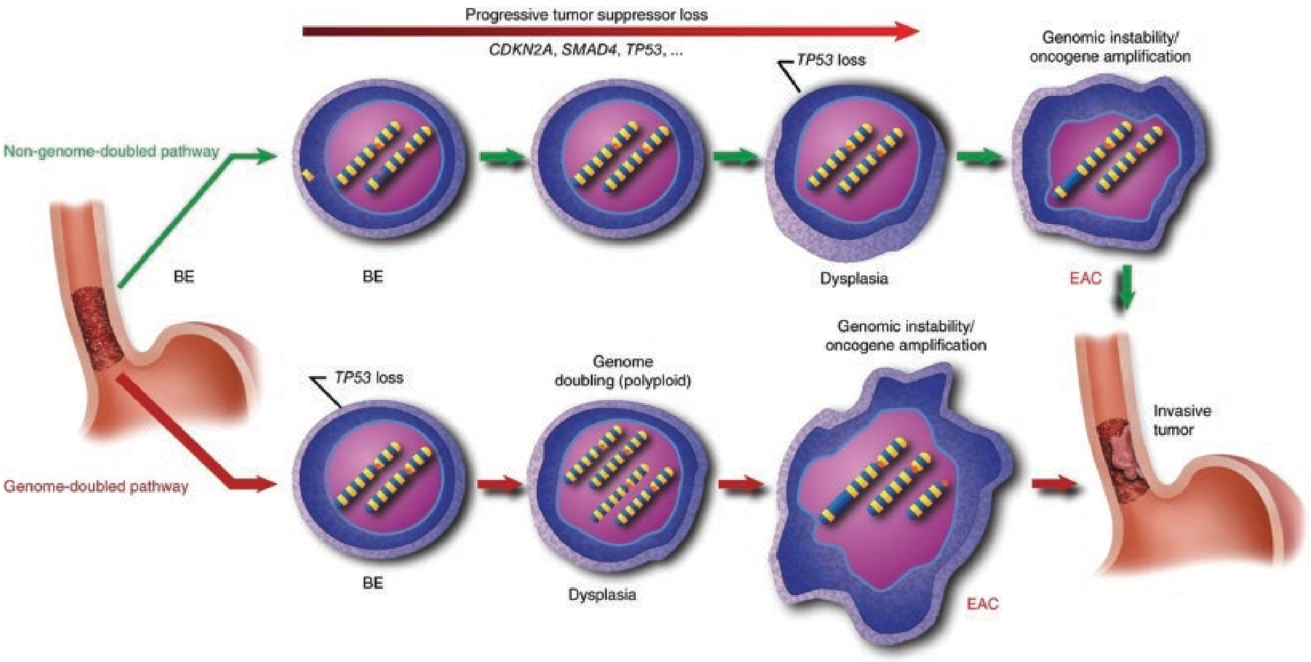

Figure 8 Genetic aberrations resulting in esophageal adenocarcinoma development. Taken, with permission, from Stachler, M., Taylor-Weiner, A., Peng, S. et al. Paired exome analysis of Barrett’s esophagus and adenocarcinoma. Nat Genet 47, 1047–1055 (2015).

may also present with anemia and melena if there is significant bleeding from the tumor. The presence of dysphagia usually suggests invasive cancer such as T3/T4 disease, while systemic symptoms like fever and weight loss indicates metastatic disease (Ripley et al. 2016). Rarely, EAC can present with tracheoesophageal fistula and/or aspiration pneumonia due to tumor erosion into the bronchial structures (Adler et al. 1985).

Esophagogastroduodenoscopy (EGD) is normally required for diagnosis. This allows for direct visual assessment of the esophagus and allows for sampling of the lesion to confirm the diagnosis. Endoscopically, BE is suspected when salmon-colored mucosa extends at least 1 cm above the gastroesophageal junction (GEJ) into the tubular esophagus and must be confirmed on histopathology assessment by the presence of intestinal metaplasia with goblet cells. Accurate description of the BE segment is vital, and the Prague C[ircumferential] & M[aximum] criteria is utilized for this purpose, taking into account the length of BE that is circumferential, as well as the total length of the segment. For surveillance of Barrett's esophagus, biopsies should be obtained according to the Seattle protocol (Fitzgerald et al. 2001), in which samples are taken in four quadrants, and separate bottles are utilized every 1–2 cm.

Since adenocarcinoma of the esophagus is almost always distal in location, it's confusion with proximal gastric adenocarcinoma has led to the Siewert classification in an attempt to distinguish between these two entities as current first line chemotherapy for gastric versus esophageal adenocarcinoma are quite different (Siewert JR, 2000 #57744). Adenocarcinoma that are predominantly found in the esophagus are Siewert Type 1; those at the gastro-esophageal junction are Type 2, and those predominantly in the stomach are Type 3's. This has implications to approach and treatment. Type 3s are usually treated like gastric cancers and undergo staging laparotomy. Type 1 and 2 are often treated like esophageal adenocarcinoma though the precise approach to Type 2 cancers have not been determined.

In patients with EAC, the endoscopic findings can be quite varied and range from subtle nodularity in intramucosal cancers to friable, fungating tumors causing complete esophageal luminal obstruction (8). In lesions that may be amenable to endoscopic resection, deep biopsies should be avoided as subsequent scarring can hinder dissection of the lesion.

It is important to note that the vast majority of EAC, which is diagnosed at late stage (Hur et al. 2013), is diagnosed without a prior diagnosis of BE (Visrodia et al. 2016). EGD can be utilized for screening in high risk populations and is most commonly performed screening procedure at this time. If pursued, documentation of the Prague C&M criteria and obtaining biopsies as per the Seattle protocol is of paramount importance. Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS-3D; CDx Diagnostics, Suffern, NY) is a novel sampling technique utilizing cytological samples obtained with a stiff brush, coupled with interpretation by a proprietary artificial intelligence neural network to highlight areas of dysplasia, assisting pathologists in the interpretation of tissue. While relatively new to the armamentarium of BE screening, data suggests this technique can increase dysplasia yield (Codipilly et al. 2022b), and thus guidelines have suggested its use in an adjunctive manner (in addition to Seattle protocol biopsies) during BE screening and surveillance (Qumseya et al. 2019). The precise role of WATS is still being defined given the lack of long-term outcomes of patients who have neoplastic disease solely diagnosed by WATS.

Less-invasive modalities are available for screening purposes. Transnasal endoscopy (TNE) can be performed at the point of care, though the use is technically more difficult than standard endoscopy because of the small diameter. TNE uses an ultrathin endoscope inserted through the nasal cavity for visual inspection of esophageal mucosa. It requires no sedation, and has good specificity and sensitivity (Honing et al. 2019). Patients tolerate this procedure well and studies suggest TNE is preferred to conventional EGD in patients willing to undergo the procedure (Sami et al. 2019a). If any suspicious lesions are found, EGD should follow for sampling. However, TNE is not widely available and often requires more preparation time in order to provide local anesthesia. Acceptance by primary care physicians and patients has been a limiting factor.

Barium esophagography may show a mass but can be normal in early-stage disease. If metastatic disease is suspected, staging proceeds with computed tomography (CT) of the chest, abdomen, and pelvis, and/or a positron emission tomography (PET). More recently, MRI has been combined with PET imaging with even higher resolution. In addition, newer nuclear agents that are more specific than standard FDG PET imaging have been able to image even more metastasis with less false positives. Standard endoscopic ultrasound (EUS) is typically done to assess for the presence of regional lymphadenopathy and to sample lymph nodes for most esophageal adenocarcinoma. For patients with early stage disease such as intra-mucosal cancer, EUS probably has less of a diagnostic role as unsuspected lymph nodes are uncommon. Endoscopic resection is generally required to establish the early nature of disease and to exclude invasion into the submucosal.

Prognosis

Staging of EAC is the most significant predictor of risk and follows American Joint Committee on Cancer guidelines (Table 1a and 1b) (Rice et al. 2017). Staging involves depth of tumor invasion (T), lymph node involvement (N), and metastatic spread (M). Staging may involve CT or PET scan to assess distal spread of the tumor. As previously described, EUS can be used to assess for locoregional lymphadenopathy. Risk factors

Table 1a Cancer staging categories for cancer of esophageal adenocarcinoma.

Category	Criteria
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis

Table 1b Clinical stage groups for esophageal adenocarcinoma.

AJCC Stage	cTNM staging
0	Tis N0 M0
IA	T1 N0 M0
IIA	T1 N1 M0
IIB	T2 N0 M0
IIIA	T2 N1 M0 T3-4a N0-1 M0
IVA	T1-4a N2 M0 T4b N0-2 M0 T1-4 N3 M0
IVB	T1-4 N0-3 M1

associated with poor survival regardless of stage of the disease include male gender, older age at diagnosis, visceral obesity, and first-degree family history of EAC. Patients with stage IV disease typically have five-year survival rates of less than 5%, whereas those with Stage I/II disease have five-year survival rates exceeding 50% (Hur et al. 2013).

Management

Significant advancements over the past 20 years, in particular the introduction and subsequent refinement of endoscopic resection coupled with ablative therapies have supplanted the use of esophagectomy for management of dysplastic BE and early stage EAC. This has avoided the significant morbidity and mortality associated with surgery and has improved long-term outcomes in the patient population. For patients with disease not amenable to endoscopic therapy, surgical techniques have evolved, and the safety of these procedures has considerably improved since their inception. Immunotherapies and targeted molecular therapies have also provided improved survival for those with metastatic disease not amenable to surgical resection. The following chapter has been divided into endoscopic therapy, surgery and chemotherapy, radiotherapy, and biological targeted therapy.

I Endoscopic Therapy

1. Dysplastic BE and T1a Disease – Endoscopic Eradication Therapy

Endoscopic eradication therapy (EET) is the first line therapeutic option for patients with BE dysplasia and early stage (T1a) EAC. EET involves the combination of endoscopic resection with ablation. Of note, the clinical management is individualized and so not every patient will require both resection and ablation; patients may need only one modality for management of their disease, though typically resection and ablation are required in cases of EAC.

It is important to note that guidelines recommend the endoscopic resection of any nodular disease found within a segment of BE (Shaheen et al. 2022).

A Endoscopic Resection

Endoscopic resection is used for nodular Barrett's Esophagus and early stage EAC. There are two primary resection techniques: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

1. Endoscopic Mucosal Resection

There are two basic methods in which EMR can be completed: one utilizes a cap with a crescent snare, while the alternative utilizes a band-ligator similar to that used for variceal banding.

In cap assisted EMR (cEMR), a hard cap (Olympus Medical, Center Valley, PA) is fitted onto the end of the endoscope. Careful assessment of the lesion of interest is carried out. A lifting agent, typically comprised of saline, epinephrine, is first injected submucosally under the lesion. This allows a “lift” of the mucosa from the submucosa. If poor lifting is noted, this may indicate deeper invasion of the lesion than expected (though this could also occur in the setting of fibrosis due to prior procedures or extensive biopsying). A crescent shaped snare (SnareMaster Crescent; Olympus Medical, Center Valley, PA) is seated on the inner aspect of the cap, followed by suction of the lesion into the cap. The snare is closed and the lesion is resected using a combination of cutting and coagulation current from an electrosurgical generator (Of note, typically the snare can be used only once).

With band-ligator EMR (blEMR), a modified banding kit is used to snare the lesion of interest (Figure 9). There are two commercially available products, the Captivator EMR (Boston Scientific, Marlborough, MA) and Duette Multi-Band Mucosectomy Device (Cook Medical, Winston-Salem, NC). Assessment of the lesion of interest and submucosal injection of the lifting agent proceeds as above for cEMR but suctioning and snaring of the lesion takes place with the fitted device. The bands are “fired,” and the lesion can then be resected by passage of an electrical snare via the working channel, and the process can then continue utilizing the next band to snare another area of interest.

Of note, specimens are limited to the size of tissue that can be sucked into the cap. Therefore, the largest lesion resected by EMR is typically around 15 mm, and lesions larger than this must be resected in piecemeal which can hinder histologic staging of the underlying tumor.

Endoscopic Submucosal Dissection (ESD)

ESD is a more recently developed endoscopic resection technique, and unlike EMR, allows complete (*en bloc*) removal of larger lesions in one piece (Figure 10). Similar to EMR, during ESD, careful inspection of the lesion, followed by thermal marking of the borders, is followed by injection of a lifting agent (again, usually a combination of saline, epinephrine, and a viscous agent such as hydroxypropylmethyl cellulose). The viscous solution is important for ESD since it is important to visualize the submucosal space for proper dissection. Once an adequate lift has been achieved, careful dissection takes place utilizing a variety of electrosurgical knives and devices. The type of device is usually dependent on the training of the endoscopist and the reimbursement environment of the country in which the procedure is performed. Many different knives are available although it appears that scissor type knives are the easiest to learn and also can perform the entire resection as well as hemostasis with only one device {Hanada and Wang, 2021 #57723}. This technique requires specialized

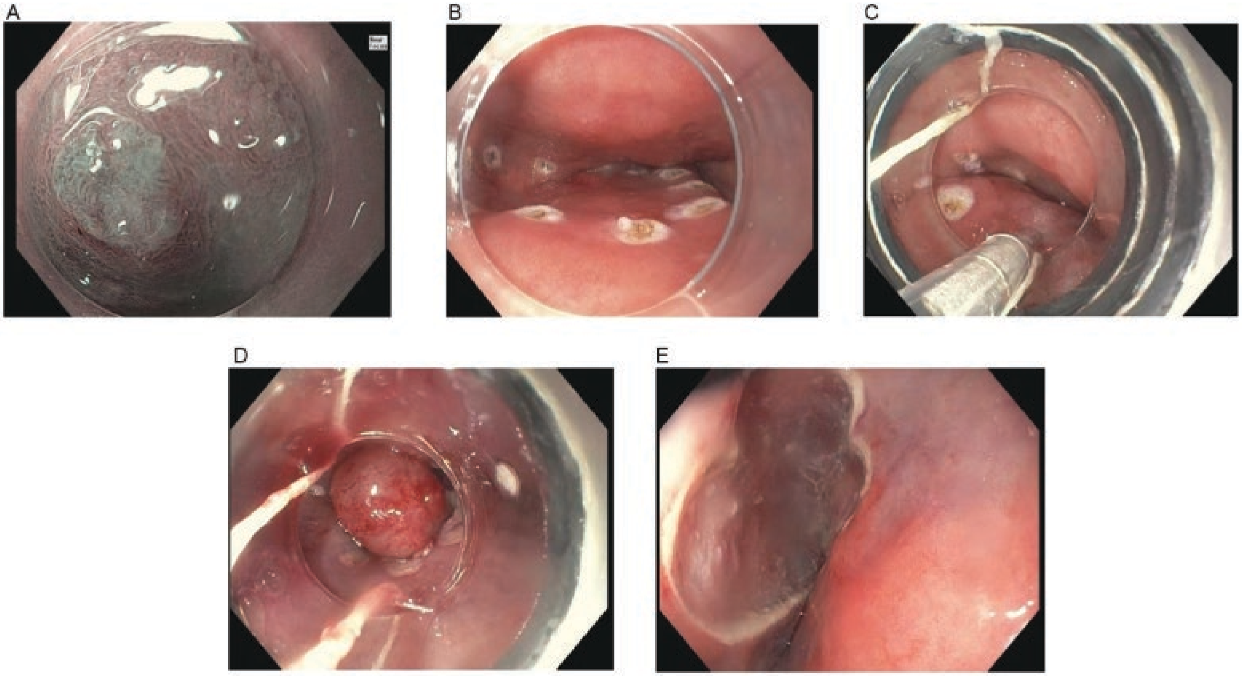

Figure 9 Band-ligation endoscopic mucosal resection. A. A nodular lesion is identified under narrow band imaging in an area of Barrett’s esophagus. B. Electrocautery is utilized to mark a clear margin around the lesion. C. A submucosal lift is obtained. D. A multiband mucosectomy kit is utilized to snare the lesion with suction, creating a pseudopolyp that is then banded and resected utilizing electrocautery. E. The post resection bed is visible after removal of the area of nodular Barrett’s esophagus.

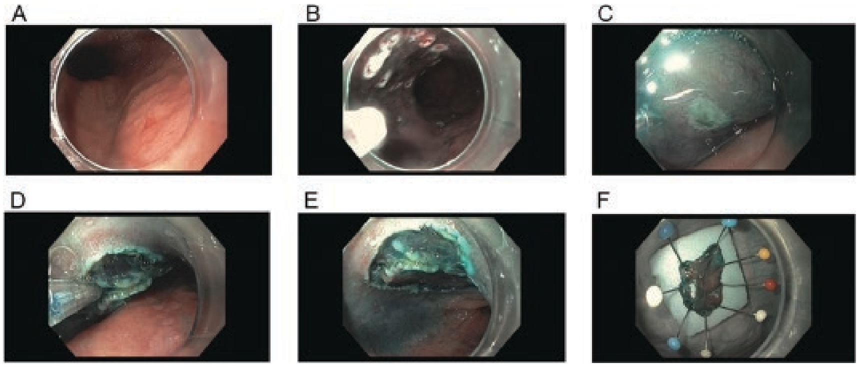

Figure 10 Endoscopic submucosal dissection. A. A nodular area is noted in Barrett's esophagus mucosa. B. The margins of the lesion are marked with cautery. C. Methylene blue saline injection in utilized to lift the lesion. D. Dissection proceeds utilizing the Hook Knife (Olympus USA, Center Valley, PA). E. The dissection bed after removal of the lesion. F. Pinning of the resected lesion to Styrofoam.

training in third-space endoscopy but once mastered yields safety profiles similar to EMR. The proceduralist separates, and ultimately removes, the mucosa and submucosa from the remainder of the esophageal wall and can send the entire specimen to pathology for review.

Advantages and Disadvantages of Endoscopic Resection Techniques

Both cEMR and ESD can result in curative resection of early-stage disease, obviating the need for esophagectomy which carries its own significant morbidity and mortality. However, there are several differences between these two techniques that must be highlighted. ESD is technically more challenging compared to cEMR, and thus requires extensive training. ESD may require as many as 250 procedures to gain competence compared to only 25 in cEMR (Yang et al. 2021; Zhang et al. 2020). As such, the ASGE recommends an intensive, "step-up" program for ESD training whereas EMR competency can be obtained during a typical gastroenterology fellowship (Maple et al. 2015). ESD is associated with considerably longer procedure times given the need for careful dissection (Terheggen et al. 2017). ESD is also associated with a higher risk of perforation compared to cEMR, though both procedures are safe given overall complication rates of less than 5% (Maple et al. 2015).

It is unclear if there is a therapeutic benefit favoring one of these procedures. A retrospective review of patients receiving EMR against those receiving ESD for dysplastic BE/IMCa demonstrated no difference in remission of intestinal metaplasia rates at two years, though remission of dysplasia occurred earlier in ESD patients possibly mediated by the removal of larger areas of BE tissue during resection (Codipilly et al. 2022a). Regardless, cEMR is recommended for lesions less than 1–1.5 cm in diameter, while ESD is recommended for larger lesions as it allows *en bloc* resection and accurate histopathological staging of the lesion with assessment of both lateral and deep margins which may ultimately affect further management.

B. Ablation

Endoscopic resection is coupled with different ablation strategies to treat the residual BE segment until eradication of intestinal metaplasia is achieved. Ablation alone can be used in the setting of dysplasia without discrete nodularity. Complete remission of intestinal metaplasia (CRIM) is associated with a lower risk of dysplasia and advanced neoplasia recurrence compared with complete remission of dysplasia (CRD) only (Sawas et al. 2019). As such, the goal for any patient entering a program for EET should be CRIM, and not CRD alone. Typically, patients return for assessment of response to therapy and potential repeat therapies every 3–4 months.

1. Radiofrequency Ablation

Radiofrequency ablation (RFA) is a minimally invasive procedure during which radiofrequency energy is applied to the esophageal epithelium causing local coagulative necrosis (Figure 11. As energy application is limited to the mucosa, there is minimal to no damage to the submucosa and deeper structures (Visrodia et al. 2017). RFA requires the use of a specialized RFA balloon which can provide circumferential energy (Halo 360 BarrX RFA Ablation Catheter, Medtronic, Minneapolis, MN) or focal catheter for targeted therapy (Halo BarrX Focal RFA Catheters, Medtronic, Minneapolis, MN).

The pivotal AIM-Dysplasia trial confirmed the efficacy of RFA in the management of dysplastic BE (Shaheen et al. 2009). In this multicenter, sham-controlled trial with 127 patients with either low-grade dysplasia (LGD) or HGD, 77.4% of patients in the ablation group achieved CRIM compared to 2.3% in the control group ($p<0.001$). Moreover, patients in the ablation group had a reduced risk of disease progression (3.6% vs. 16.3%, $P=0.03$) and experienced fewer cancers (1.2% vs. 9.3%, $P=0.045$).

Given that the risk of LGD progression is considerably lower than that associated with HGD, Phoa et al. conducted a randomized controlled trial to assess the efficacy of

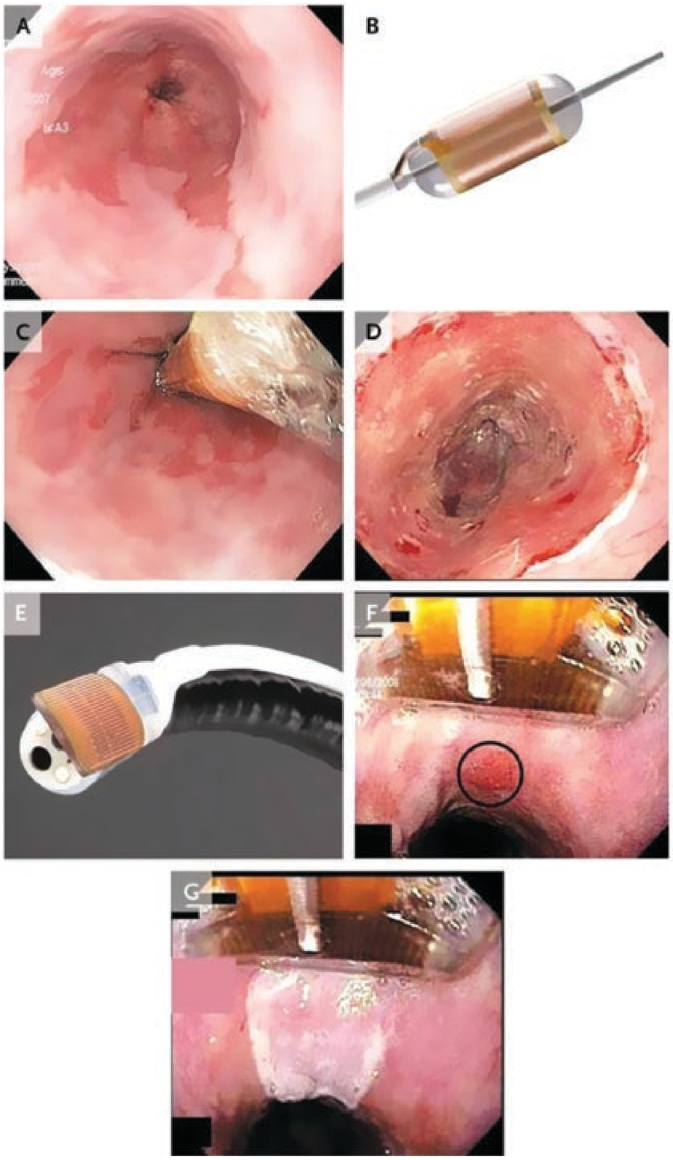

Figure 11 Radiofrequency ablation (RFA). A. An area of Barrett's esophagus (BE) is identified endoscopically. B. Image of the Halo 360 BarrX radiofrequency catheter (Medtronic USA, Minneapolis, MN). C. Positioning of the catheter over the area of BE prior to balloon insufflation. D. Post-ablation view of mucosa shows proper treatment effect. E. Focal Halo BarrX radiofrequency catheter (Medtronic USA, Minneapolis, MN) attached to endoscope. F. Area of suspicious BE mucosa is circled. Note the ablation device at the 12 o'clock position. G. Appropriate post-ablation changes.

ablation against endoscopic surveillance in patients with LGD. This multicenter trial followed 135 LGD patients and determined that RFA reduced the risk of progression to HGD/EAC by 25% ($p<0.001$) and risk of progression to EAC alone by 7.4% ($p=0.03$) (Phoa et al. 2014). Furthermore, 88.2% achieved CRIM in the ablation group compared to 0.0% in the surveillance group ($p<0.001$).

In both trials, RFA was relatively safe and the most common adverse effects were stricture and bleeding, both of which were managed either endoscopically or conservatively. Of note, patients did report higher chest pain scores after the procedure and in clinical practice, patients may require home-going analgesics for several days after RFA.

Long-term follow-up demonstrates persisting efficacy and low intestinal metaplasia recurrence rates in patients treated with RFA for BE-dysplasia or early stage T1a treated with RFA (Phoa et al. 2016; van Munster et al. 2021; Wolfson et al. 2022).

2. Cryotherapy

Cryoablation is a controlled, localized freezing technique which induces tissue injury via rapid intracellular freezing causing cell necrosis (Johnston et al. 1999). Although RFA is generally considered first line ablative therapy for management of dysplastic BE, cryoablation is gaining newfound appreciation.

Cryoablation currently has two delivery systems, one via a cryoablation balloon and one via spray cryotherapy. In cryoballoon ablation (C2 Cryoballoon System; Pentax Medical Corporation USA, Montvale, NJ), an inflatable balloon is passed via the working channel of a therapeutic endoscope. Within this balloon is a spray port that can be manipulated with 360° of freedom and also positioned at any point along the length of the balloon allowing for precise targeting of lesions of interest. Under direct endoscopic visualization, cryogen is sprayed on the inner surface of the balloon which is in approximation to the lesion on the outer surface of the balloon for approximately 5–10 seconds (Canto et al. 2020). The balloon can be repositioned as needed to target multiple areas.

In spray cryotherapy (truFreeze Spray Cryotherapy System, Steris Corp., Mentor, OH), liquid nitrogen and/or argon gas are used to deliver cryogen therapy directly to the tissue. Given the large amount of gas that is utilized to provide this spray, placement of an orogastric tube connected to suction is required to vent the insufflated air from the stomach. The proceduralist then directs the spray catheter and applies the cryogen directly to the lesion of interest. Spray cryotherapy utilizes several freeze-thaw cycles to induce tissue necrosis.

Cryotherapy was initially utilized as a second-line therapy for patients who did not respond to initial RFA. Assuredly, a systematic review and meta-analysis in patients receiving cryotherapy as salvage therapy after RFA failure demonstrated CRIM achievement rates of 45.9% (95% CI: 32.0–60.5%) (Visrodia et al. 2018).

Retrospective data on a cohort of patients receiving either RFA (226 patients) or cryoballoon ablation (85 patients) as primary ablative therapy for EET demonstrated no difference on CRD or CRIM rates at two years (Agarwal et al. 2021). Furthermore, cryoablation is safer and better tolerated compared to RFA, inducing less chest discomfort and fewer strictures after therapy (Agarwal et al. 2021; Visrodia et al. 2018). As such, cryoablation may be a reasonable alternative for first line ablative management of dysplastic BE/IMCa.

3. Argon Plasma Coagulation and Bipolar Cautery

Argon plasma coagulation (APC) is a noncontact thermal technique where an ablation probe is introduced via the working channel of an endoscope and thermal energy is transferred to the target tissue via ionized argon gas without any direct contact with the tissue. Bipolar electrocautery is one of the earlier technologies used to ablate Barrett's esophagus and utilizes the passage of current through tissue to induce necrosis. In bipolar cautery, the electrode needs to be in contact with the mucosa to be effective (Dumot and Greenwald 2008). Both of these techniques can be utilized to treat focal areas of residual Barrett's mucosa, and no data exist to suggest that one method is superior to the other. Though currently these are used only to treat residual areas of Barrett's esophagus, initially these techniques were used to treat the entire segment though these procedures were much more tedious to perform and usually involved non-uniform injury to the mucosa since the devices are "point" devices developed to treat small areas of bleeding in the gastrointestinal tract.

Long-term Recurrence after EET

Surveillance intervals once CRIM is achieved following RFA are currently not evidence based. Two large, multicenter, retrospective reviews assessed recurrence of BE following CRIM and found cumulative intestinal metaplasia recurrence rates ranging from 19–33% within two years of achieving CRIM (Gupta et al. 2013; Sami et al. 2019b).

Notably, the majority (approximately 75%) of recurrences develop at the gastroesophageal junction (GEJ) while the remainder are found in the tubular esophagus (Sami et al. 2019b). Increased risk of recurrence was found in patients with baseline dysplasia or intramucosal carcinoma, long-segment BE (> 3 cm), and RFA treatment performed at low volume centers (Krishnamoorthi et al. 2016).

Consequently, most proceduralists surveil CRIM patients every 3–6 months for the first year, then extend surveillance intervals depending on the histological and clinical scenario.

T1b Disease

T1b disease, that is, disease that invades no deeper than the submucosa, has traditionally been managed with surgical resection allowing for lymph node dissection to assess for locoregional metastasis. However, recent evidence indicates that in patients with low-risk T1b (that is, patients with *en bloc* tumor resection, R0 margins, absence of lymphovascular invasion, and well or moderately differentiated disease), EET may carry comparable outcomes as surgery though with less peri-procedural complications. Studies have demonstrated that these low-risk T1b patients treated endoscopically have similar cancer-free survival, remission, recurrence, and remission rates compared to low-risk T1b patients treated surgically (Ballard et al. 2016; Manner et al. 2008). Recent guidance from the American Gastroenterology Association suggests that low risk T1b patients should be offered endoscopic therapy as a potential curative therapy (Motomura D 2021). As such, it is reasonable to "consider" the use of EET in low-risk T1b lesions, though in clinical practice multidisciplinary management is strongly recommended to develop a strategy for individual patients based on their comorbidities and expectations.

Palliative Management

In patients with heavy disease burden and incurable disease, palliation is an important aspect of care to improve quality of life. While non-curative intent esophagectomy can be pursued in selected patients, this is rarely done given the complexity and morbidity of this surgery. For patients with considerable dysphagia, as well as those with slow, oozing blood loss from a tumor, endoscopic stenting can relieve obstruction or provide tamponade in patients with inoperable esophageal cancer

(Madhusudhan et al. 2009). However, patients frequently will experience chest discomfort when a stent is in place and this may limit acceptability. Spray cryotherapy can also be used as palliative therapy and may delay the need for stenting by more than a year (Hanada et al. 2022).

II Surgical Treatment of Esophageal Adenocarcinoma

Indications

Surgery, in the form of an esophagectomy, plays an important role in the treatment of esophageal adenocarcinoma. Most commonly, surgical treatment is indicated in patients with locoregional limited esophageal adenocarcinoma as part of multimodality therapy in combination with neoadjuvant chemoradiation or perioperative chemotherapy. This includes patients with clinical stages IIA to IVA disease, except those with T4b tumors (i.e. direct invasion to aorta, trachea, or vertebral body) or with extensive N3 disease (i.e. 7 or more lymph nodes) that is deemed unresectable. Surgical treatment can also play a role in the management of early-stage esophageal adenocarcinoma (T1 lesions). Although endoscopic resections are currently favored for lesions limited to the mucosa (Tis and T1a), surgery can be considered in T1a tumors exhibiting high-risk features such as poor grade of differentiation or lymphovascular invasion in the endoscopic resection specimen, due to their association with higher rates of regional lymph node involvement. In addition, surgery is indicated in cases with positive vertical margins after endoscopic resection. In cases invading the submucosa (T1b), surgery is preferred given the high risk of regional lymph node involvement. In cases of T1 tumors, upfront surgery without neoadjuvant therapy is favored. Esophagectomy for high-grade dysplasia is rare and every effort should be made to preserve the esophagus. If faced with a case of high-grade dysplasia that cannot be eradicated endoscopically, one must balance the risks and benefits of an esophagectomy, and the least invasive approach should be carried. An extensive lymphadenectomy can be omitted in those cases to mitigate the perioperative risk. Currently, surgery does not play a routine role in the treatment of metastatic esophageal adenocarcinoma, even if oligometastatic. However, palliative resection can be considered on an individual basis but there are almost always better less aggressive alternatives (radiation, stents, endotherapy, systemic treatment). Finally, surgery is not favored as a primary treatment in patients with non-regional lymph node involvement (e.g. retroperitoneal lymph nodes, supraclavicular lymph nodes in cases of distal and gastroesophageal junction adenocarcinoma). However, in selected patients with non-regional nodal involvement or oligometastases (single organ metastases) that show a good response to induction chemotherapy, surgery may still be a realistic option (Schizas D et al. World J Surg Oncol 2018; Depypere L et al. Dis Esophagus, 2017; Toxopeus E et al. EJSO, 2015).

Preoperative Evaluation

An esophagectomy is a complex procedure that historically has been associated with significant perioperative morbidity. Therefore, a thorough preoperative evaluation is critical. Besides adequate staging to ensure the resectability of all diseases, it is important to determine whether the patient has sufficient cardiopulmonary reserve to tolerate the operation. A comprehensive history should inquire about symptoms suggestive of angina, heart failure or poor overall functional status. Cardiac evaluation must consider a stress test and coronary angiography, if indicated. In addition, all patients should undergo pulmonary function testing as the results of the forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLCO) are associated with perioperative risk and determine the capacity of the patient to tolerate single-lung ventilation during an esophagectomy. Esophagectomy should be considered carefully in patients over 80 years old due to higher rates of postoperative morbidity and mortality(1). Finally, a nutritional evaluation must be completed. Almost all patients with locoregional esophageal cancer have some degree of dysphagia and weight loss on presentation. Some patients might benefit from a preoperative feeding tube (e.g., nasogastric, nasojejunal, or surgical jejunostomy tube) to support them through neoadjuvant therapy. Patients with an albumin level <3.5 g/dL and/or prealbumin level <15 mg/dL should be aggressively optimized from a nutritional standpoint before proceeding with an operation.

Types of Esophagectomy

There are different types of esophagectomy. The type of esophagectomy to be performed depends mostly on three factors: tumor location, conduit availability for reconstruction, and surgeon preference/experience. Reconstruction with a gastric conduit is routinely favored whenever feasible as it has better long-term functional outcomes. An Ivor Lewis esophagectomy refers to a two-staged operation with an abdominal stage for mobilization of the stomach, creation of a gastric conduit, and intra-abdominal lymphadenectomy, followed by a right thoracic stage with mobilization and transection of the esophagus, mediastinal lymphadenectomy, and creation of an intrathoracic esophagogastric anastomosis. A three field or McKeown esophagectomy refers to a three-staged operation starting with a right chest approach for mobilization of the entire thoracic esophagus and mediastinal lymphadenectomy, followed by an abdominal stage as described above, and finishing with a left neck exploration for mobilization and transection of the cervical esophagus and creation of an esophagogastric anastomosis in the neck. See chapter on ESCC, for more details on nodal stations and nodal dissection. These two types of esophagectomy are currently preferred as they allow for direct dissection of the tumor and adequate abdominal and mediastinal lymphadenectomy. Other types of esophagectomy include the transhiatal esophagectomy that refers to a two-staged operation with an abdominal and left neck stage as described earlier, with dissection of the thoracic esophagus through the diaphragmatic hiatus which hampers the ability to perform an intrathoracic lymphadenectomy. Transhiatal esophagectomy however is associated with a lower risk for postoperative complications and may be indicated in frail patients when the risk for nodal metastases in the middle and upper mediastinum is low such as in junctional cancers (Omloo J et al. Ann Surg 2007). Finally, a left thoracoabdominal esophagectomy is now rarely indicated in the management of esophageal cancer, and mostly reserved for the management of Siewert III gastroesophageal junction tumors requiring total gastrectomy.

Most cases of esophageal adenocarcinoma are in the distal esophagus or gastroesophageal junction (Siewert I or II tumors), in which an Ivor Lewis esophagectomy is favored. As discussed in the chapter 5 on ESCC, esophagectomy for SCC is mostly performed via a three stage (McKeown) approach. Preferentially, this is performed using a minimally invasive technique (combined laparoscopy and video-assisted thoracoscopic surgery – VATS, with or without robotic assistance). A minimally invasive Ivor Lewis esophagectomy allows excellent visualization of mediastinal structures, a complete lymph node dissection, and a tension-free anastomosis, while minimizing recurrent laryngeal nerve injuries. In cases of adenocarcinoma extending to the mid esophagus, a three field McKeown esophagectomy must be considered to ensure adequate proximal margins of resection of at least 4–5 cm. In all cases, a thorough abdominal and intra-thoracic lymphadenectomy are recommended. This is also true for cases of T1a disease, as in the presence of high-risk features or deep margins prompting esophagectomy, the risk of regional lymph node involvement is higher and adequate regional lymph node evaluation is of utmost importance to adequately stage patients to determine the potential need for adjuvant therapy. In the rare instances when the stomach is not available to be used as a conduit for primary reconstruction of the gastrointestinal tract, options include reconstruction with long segment supercharged pedicled jejunal interposition or colon interposition (2).

Postoperative Care

Routine postoperative care includes extubation in the operating room. Patients are kept on a monitored bed for one night. Multimodal analgesia techniques are used after minimally invasive esophagectomy, including intercostal nerve blocks, acetaminophen, ketorolac, and patient-controlled analgesia with opioids. Enhanced recovery after surgery (ERAS) postoperative pathways are encouraged. If a jejunostomy tube is present, tube feeds can start on postoperative day 1 or 2. A nasogastric tube is removed on postoperative day 3 to 5. A contrast esophagram and pleural fluid amylase levels can be used to detect anastomotic leaks before initiation of oral intake. Patients are usually discharged from the hospital approximately on postoperative day 7.

Results and Complications

Esophagectomy can be performed safely. The overall postoperative complication rate is approximately 60% based on data from the Society of Thoracic Surgeons General Thoracic Surgery Database and the Esophageal Complications Consensus Group (3, Low D. et al. Ann Surg 2019). Major postoperative complications include anastomotic complications represented by anastomotic leaks (12%; although only 7% require intervention) and gastric conduit necrosis (2%). Respiratory complications are frequent and occur in approximately 26% of patients. These include pneumonia (12%), acute respiratory distress syndrome (4%), need for initial invasive ventilatory support (4%), need for a tracheostomy (6%), pneumothorax (2%), pulmonary embolism (1.5%), among others. Infectious complications include surgical site infection (6%), sepsis (5%), and empyema (2%). Other notable complications after esophagectomy are chylothorax (3%), cardiovascular events (2–3%), gastric outlet obstruction (1%) and recurrent laryngeal nerve injury (4%) (3). Recurrent laryngeal nerve injuries are significantly more frequent after three field McKeown esophagectomy due to dissection in the left neck and can be observed in up to 8% of cases versus 1% after Ivor Lewis esophagectomy (4, van Workum F. et al. JAMA Surg 2021). Postoperative mortality has been reported to occur in up to 3% of cases. Table 4 in the chapter on surgical management of ESCC summarized morbidity and mortality after esophagectomy in recent large RCTs. Morbidity and mortality vary by institution, with better outcomes associated with higher hospital volume.

The use of minimally invasive techniques in esophagectomy has been associated with a lower incidence of postoperative complications. A recent clinical trial randomized 207 patients to either hybrid Ivor Lewis esophagectomy (abdominal stage with laparoscopy and thoracic stage with thoracotomy) or open esophagectomy (laparotomy and thoracotomy) (5). The authors found that a hybrid esophagectomy including minimally invasive techniques was associated with a 77% lower risk of major intraoperative and postoperative complications when compared to an open procedure, including a 50% lower risk of pulmonary complications, without compromising long-term overall and disease-free survival. Another randomized clinical trial of 115 patients, showed that minimally invasive esophagectomy was associated with better quality of life scores at one year after surgery when compared to open esophagectomy (6). A minimally invasive esophagectomy (Ivor Lewis or McKeown) can be performed successfully in most patient with very low rates of conversion to an open procedure (<5%) (4). Complete resection (i.e., R0, negative margins) can be accomplished in 98% of cases. The median lymph node harvest is 21 lymph nodes. A recent randomized controlled trial showed that robot-assisted thoracolaparoscopic esophagectomy was associated with a lower rate of surgery-related postoperative complications compared to open esophagectomy (van der Sluis P. et al. Ann Surg 2019).

III Chemotherapy, Radiation Therapy, and Immunotherapy

Localized Disease

Only 30–40% of patients with esophageal cancer have potentially resectable disease at presentation and the outcome of these patients is generally poor when treated with surgery alone (Zhang, 2013; Hulscher et al. 2002). Most surgical series report five-year survival rates of around 40% when treated with surgery alone (Rice et al. 2009). Various combined modality approached have therefore been explored to improve outcome of these patients. Several trials have demonstrated a better survival with preoperative chemoradiotherapy compared with surgery alone in patients with stage T3/T4 or node-positive localized disease (Chan et al. 2018). Preoperative treatment is currently recommended for all clinical stage 2 and above resectable esophageal tumors. The optimal treatment for clinical T2N0 adenocarcinoma of the esophagus is still debated, although clinical guidelines such as the NCCN prefer upfront chemoradiotherapy in this patient group.

The largest and most important trial comparing preoperative chemoradiotherapy with surgery alone is the Dutch CROSS trial (Van Hagen et al. 2012). In this trial 363 patients (including 273 with adenocarcinoma) were randomized to chemoradiotherapy using weekly paclitaxel (50 mg/m^2) plus carboplatin (AUC 2) with concurrent radiotherapy (41.4 Gy over five weeks) or surgery alone. The two year overall survival increased from 50% for patients who underwent surgery alone to 67% for patients treated with the multimodal approach (Van Hagen, et al. 2012). This survival benefit persisted with longer follow-up for at least 10 years (Eyck et al. 2021). Ever since, the CROSS regimen has been widely adopted as one of the standards of care for localized resectable esophageal cancer. A large meta-analysis confirmed the benefit of neoadjuvant chemoradiotherapy versus surgery alone in patients with adenocarcinoma of the esophagus or gastro-esophageal junction (HR 0.75, 95% CI 0.59–0.95) (Sjoquist et al. 2011). Although 25% of patients with esophageal adenocarcinoma have a complete pathological response after neo-adjuvant chemoradiotherapy, inclusion of surgery is still standard of care. However, for patients who are no surgical candidates definitive chemoradiotherapy is also a reasonable approach.

It's still unclear whether adding radiotherapy to neoadjuvant chemotherapy is superior to neoadjuvant chemotherapy alone for the treatment of localized esophageal adenocarcinomas. Most randomized trials and a recent meta-analysis have failed to demonstrate a survival benefit for preoperative chemoradiotherapy over chemotherapy alone (Deng et al. 2017; Fan et al. 2021). Distal cancers of the esophagus and the gastro-esophageal junction (GEJ) were also included in landmark trials for the treatment of localized gastric cancer such as the MAGIC trial (11% distal esophageal, 15% GEJ) and the FLOT4-AIO trial (23% GEJ Siewert type 1, 33% GEJ Siewert type 2 and 3) (Cunningham et al. 2006; Al-Batran et al. 2019). First, the MAGIC trial showed a survival benefit of perioperatively ECF/ECX (epirubicine, 5-FU, cisplatin) versus surgery alone (Cunningham et al. 2006). Many years later, this chemotherapy schedule was compared with the FLOT regimen (5-FU, docetaxel, oxaliplatin) perioperatively in the FLOT4 trial and showed a survival benefit in favor of the FLOT regimen (Al-Batran et al. 2019). Until results of a trial comparing CROSS with FLOT will be available, perioperative chemotherapy remains a valid therapeutic option especially for tumors of the GEJ.

The type of adjuvant treatment depends on the neo-adjuvant strategy that was followed in patients with esophageal adenocarcinoma. For patients with primary resection, but node positive or pathologic T3 or T4, both adjuvant chemoradiotherapy or chemotherapy alone is a reasonable option as there are no randomized trials showing superiority of either approach. Patients with a residual disease after neo-adjuvant chemoradiotherapy should be treated with adjuvant nivolumab based on results from the Checkmate 577 trial (Kelly et al. 2021). In this trial 794 esophageal cancer patients (71% adenocarcinoma) were randomly assigned to nivolumab for one year or placebo and showed a median disease-free survival that was doubled in the nivolumab group (22, 4 vs 11 months).

Metastatic Disease

More than 50% of patients with esophageal or gastro-esophageal junction cancer have metastatic disease at time of diagnosis. Several therapeutic options are available for the palliative treatment of metastatic esophageal adenocarcinoma. A recent meta-analysis of trials comparing chemotherapy with best supportive care confirmed there was a significant benefit in overall survival in favor of chemotherapy (Janmaat et al. 2017). To control local symptoms palliative surgical resection (or bypass), radiotherapy or endoscopic techniques are possible therapeutic options but the decision making should take into account the limited overall prognosis of these patients.

The choice of first line systemic treatment should be based on biomarker expression. All patients should have their tumors assessed for human epidermal growth factor receptor 2 (HER2) overexpression and/or gene amplification, deficient mismatch repair status and overexpression of the programmed cell death ligand 1 (PD-L1). For patients with

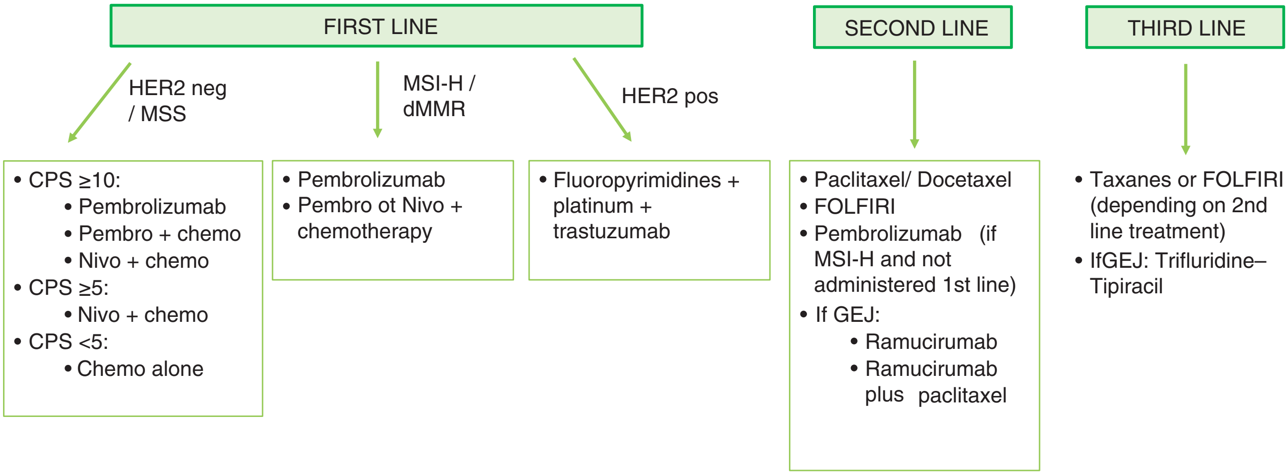
FIRST LINE
SECOND LINE
THIRD LINE
HER2 neg / MSS
MSI-H / dMMR
HER2 pos
• CPS ≥10:
• Pembrolizumab
• Pembro + chemo
• Nivo + chemo
• CPS ≥5:
• Nivo + chemo
• CPS <5:
• Chemo alone
• Pembrolizumab
• Pembro ot Nivo + chemotherapy
• Fluoropyrimidines + platinum + trastuzumab
• Paclitaxel/ Docetaxel
• FOLFIRI
• Pembrolizumab (if MSI-H and not administered 1st line)
• If GEJ:
• Ramucirumab
• Ramucirumab plus paclitaxel
• Taxanes or FOLFIRI (depending on 2nd line treatment)
• IfGEJ: Trifluridine–Tipiracil

Figure 12 Chemotherapeutic options for the treatment of metastatic esophageal adenocarcinoma.

HER2 overexpressing adenocarcinoma of the esophagus or junction (defined by 3+ immunohistochemistry (IHC) staining or amplification by fluorescence in situ hybridization), trastuzumab in combination with a platinum-based chemotherapy backbone is the standard treatment option based upon the TOGA trial (Bang et al. 2010). Although the ToGA trial was performed with cisplatin/fluoropyrimidine as a chemotherapy backbone, many clinicians prefer to use the FOLFOX regimen given the lower toxicity (Ter Veer et al. 2018). In patients with deficient mismatch repair (dMMR) or microsatellite instability (MSI-H), first line immunotherapy either as pembrolizumab monotherapy or nivolumab or pembrolizumab in combination with chemotherapy are acceptable options. A post-hoc analysis of the KEYNOTE-062, restricted to a subset of 50 patients with dMMR/MSI-H treated with either pembrolizumab alone or chemotherapy alone, showed a higher objective response rate, higher PFS and longer overall survival for the patients treated with pembrolizumab monotherapy (Chao et al. 2021). Combination therapy with nivolumab plus chemotherapy is another option in dMMR/MSI-H tumors, based on a subset analysis of the CheckMate 649 trial. Among the 44 patients who were randomized to chemotherapy plus nivolumab, median survival was 38.7 months (versus 12.3 months with chemotherapy alone) (Shitara et al. 2022). First line therapy with an immune checkpoint inhibitor alone or in combination with chemotherapy has also been shown to improve outcomes versus cytotoxic chemotherapy in PD-L1 overexpressing tumors. The phase 3 CHECKMATE 649 study evaluated nivolumab plus chemotherapy (FOLFOX or XELOX) versus chemotherapy alone in patients with HER2 negative, advanced esophageal, gastric, and gastro-esophageal adenocarcinoma and showed a significant improvement in overall survival, with the greatest magnitude seen in patients with high PD-L1 expression, defined by a combined positive score (CPS) of ≥ 5 (Shitara et al. 2022; Janjigian et al. 2021). In the phase 3 KEYNOTE-590 trial combination of chemotherapy with pembrolizumab significantly improved survival over chemotherapy alone in patients with esophageal or gastro-esophageal junction cancers regardless of their PD-L1 expression (Sun et al. 2021). However, the results were driven more by the squamous cell carcinoma than the adenocarcinoma. When stratified according to PD-L1 expression, the benefit was exclusively seen in the patients with a CPS ≥ 10. Monotherapy with pembrolizumab is an alternative option for patients with a CPS ≥ 10 based on the phase 3 KEYNOTE-062 trial that showed superior outcome comparing pembrolizumab monotherapy with chemotherapy alone (17.4 versus 10.8 months) (Shitara et al. 2020). This approach is however not preferred in bulky disease given the low expected response rate. The benefit of immunotherapy for adenocarcinoma of the esophagus with low levels of PD-L1 (CPS <5) is still uncertain.

The goal of second-line therapy for metastatic esophageal cancer is palliating symptoms and improving survival. The use of second line chemotherapy has been shown to improve survival when compared with best supportive care (Tomita et al. 2020). Chemotherapeutic options include taxanes or irinotecan-based chemotherapy. Patients with tumors of the gastroesophageal junction can also be treated like gastric cancer with either the VEGFR-2 inhibitor ramucirumab (with or without paclitaxel) or trifluridine-tipiracil (TAS102) (Fuchs et al. 2014; Wilke et al. 2014; Shitara et al. 2018).

Key Take Home Messages

1 Risk factors for esophageal adenocarcinoma (EAC) include Barrett's Esophagus (BE), Gastroesophageal reflux disease (GERD), central obesity, male gender, tobacco use, and family history of EAC.

2 Barrett's esophagus is identified by columnar lined mucosa in a mosaic pattern or with sub mucosal oesophageal glands (or the presence of incomplete intestinal metaplasia in the USA). There can be additional presence of either low grade or high grade dysplasia characterized by nuclear atypia and increased nuclear cytoplasm ratio.

3 Any form of unequivocal dysplasia should be removed.

4 Therapy for EAC includes endoscopic resection, surgery, or chemoradiotherapy, depending on the stage at diagnosis.

5 Surgical esophagectomy has evolved to include traditional open esophagectomy to including minimally invasive and robotic resection.

6 Immunomodulatory and molecular targeted therapies may herald a new paradigm in the treatment of EAC.

Areas for Further Research

The long-term outcome of endoscopic therapeutic techniques for early cancer resection needs further clarification.

The best combinational targeted therapy regimens including PD and PD-L1 are yet to be elucidated.

The best palliative approaches needs head to head RCTs.

Trusted WebSites for Further Reading

https://www.macmillan.org.uk/cancer-information-and-support/oesophageal-cancer/treatment-for-oesophageal-cancer

https://www.cancer.gov/types/esophageal/hp/esophageal-treatment-pdq

https://digestivecancers.eu/gastric-oesophageal-cancer-targeted-therapy-2

References

Abraham, S.C., Krasinskas, A.M., Correa, A.M. et al. (2007). Duplication of the muscularis mucosae in Barrett esophagus: an underrecognized feature and its implication for staging of adenocarcinoma. *Am J Surg Pathol* 31 (11): 1719–1725. doi: 10.1097/PAS.0b013e318093e3bf.

Adler, L., Kabnick, E.M., Patel, M. et al. (1985). Tracheoesophageal fistula secondary to esophageal carcinoma presenting with aspiration pneumonia. *J Natl Med Ass* 77: 401–403.

Agarwal, S., Alshelleh, M., Scott, J. et al. (2021). Comparative outcomes of radiofrequency ablation and cryoballoon ablation in dysplastic Barrett's esophagus: a propensity score-matched cohort study. *Gastrointest Endosc* 95 (3): 422–431.e2.

Arnold, M., Ferlay, J., Van Berge Henegouwen, M.I., and Soerjomataram, I. (2020). Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut* 69: 1564.

Badreddine, R.J., Prasad, G.A., Lewis, J.T. et al. (2010). Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma. *Clin Gastroenterol Hepatol* 8 (3): 248–253. doi: 10.1016/j.cgh.2009.11.016.

Ballard, D.D., Choksi, N., Lin, J. et al. (2016). Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection. *World J Gastrointest Endosc* 8: 763–769.

Bennett, C., Vakil, N., Bergman, J. et al. (2012 August). Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterolgoy* 143 (2): 336–346.

Bennett, C., Moayyedi, P., Corley, D.A. et al. (2015 May). BOB CAT Consortium. BOB CAT: a large-scale review and Delphi consensus for management of Barrett's Esophagus with no Dysplasia, Indefinite for, or Low-Grade Dysplasia. *Am J Gastroenterol* 110 (5): 662–682.

Brown, I.S., Whiteman D.C., and Lauwers, G.Y. (2010). Foveolar type dysplasia in Barrett esophagus. *Mod Pathol* 23 (6): 834–843. doi: 10.1038/modpathol.2010.59.

Canto, M.I., Trindade, A.J., Abrams, J. et al. (2020). Multifocal cryoballoon ablation for eradication of Barrett's esophagus-related neoplasia: a prospective multicenter clinical trial. *Off J Am College Gastroenterol | ACG* 115.

Codipilly, D.C., Dhaliwal, L., Oberoi, M. et al. (2022a). Comparative outcomes of cap assisted endoscopic resection and endoscopic submucosal dissection in dysplastic Barrett's Esophagus. *Clin Gastroenterol Hepatol* 20: 65–73.e1.

Codipilly, D.C., Krishna Chandar, A., Wang, K.K. et al. (2022b). Wide-area transepithelial sampling for dysplasia detection in Barrett's esophagus: a systematic review and meta-analysis. *Gastrointest Endosc* 95: 51–59.e7.

Codipilly, D.C., Sawas, T., Dhaliwal, L. et al. (2021). Epidemiology and outcomes of young-onset esophageal adenocarcinoma: an analysis from a population-based database. *Cancer Epidemiol Biomarkers Prev* 30: 142–149.

Dulak, A.M., Stojanov, P., Peng, S. et al. (2013). Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat Genet* 45: 478–486.

Dumot, J.A. and Greenwald, B.D. (2008). Argon plasma coagulation, bipolar cautery, and cryotherapy: ABC's of ablative techniques. *Endoscopy* 40: 1026–1032.

Dunbar, K.B., and Spechler, S.J. (2012). The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol* 107 (6): 850–863. doi: 10.1038/ajg.2012.78.

Endoscopic Classification Review Group (2005). Update on the paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* 37 (6): 570–578. doi: 10.1055/s-2005-861352.

Estrella, J.S., Hofstetter, W.L., Correa, A.M. et al. (2011). Duplicated muscularis mucosae invasion has similar risk of lymph node metastasis and recurrence-free survival as intramucosal esophageal adenocarcinoma. *Am J Surg Pathol* 35 (7): 1045–1053. doi: 10.1097/PAS.0b013e318219ccef.

Fitzgerald, R.C., Di Pietro, M., Ragunath, K. et al. (2014). British society of gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 63: 7–42.

Fitzgerald, R.C., Saeed, I.T., Khoo, D. et al. (2001). Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. *Dig Dis Sci* 46: 1892–1898.

Glickman, J.N., Chen, Y.Y., Wang, H.H. et al. (2001). Phenotypic characteristics of a distinctive multilayered epithelium suggests that it is a precursor in the development of Barrett's esophagus. *Am J Surg Pathol* 25 (5): 569–578. doi: 10.1097/00000478-200105000-00002.

Gupta, M., Iyer, P.G., Lutzke, L. et al. (2013). Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US multicenter Consortium. *Gastroenterology* 145: 79–86.e1.

Hanada, Y., Leggett, C.L., Iyer, P.G. et al. (2022). Spray cryotherapy prevents need for palliative stenting in patients with esophageal cancer-associated dysphagia. *Dis Esophagus* 35. doi:10.1016/j.gie.2020.07.037

Hanada, Y., and Wang, K.K. (2021). Safety and feasibility of same-day discharge after esophageal endoscopic submucosal dissection. *Gastrointest Endosc* 93 (4): 853–860. doi: 10.1016/j.gie.2020.07.037.

Honing, J., Kievit, W., Bookelaar, J. et al. (2019). Endosheath ultrathin transnasal endoscopy is a cost-effective method for screening for Barrett's esophagus in patients with GERD symptoms. *Gastrointest Endosc* 89: 712–722.e3.

Hur, C., Miller, M., Kong, C.Y. et al. (2013). Trends in esophageal adenocarcinoma incidence and mortality. *Cancer* 119: 1149–1158.

Hvid-Jensen, F., Pedersen, L., Drewes, A.M. et al. (2011). Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 365 (15): 1375–1383. doi: 10.1056/NEJMoa1103042.

Johnston, C.M., Schoenfeld, L.P., Mysore, J.V., and Dubois, A. (1999). Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. *Gastrointest Endosc* 50: 86–92.

Kerkhof, M., van Dekken, H., Steyerberg, E.W. et al. (2007). Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. *Histopathology* 50 (7): 920–927. doi: 10.1111/j.1365-2559.2007.02706.x.

Krishnamoorthi, R., Singh, S., Ragunathan, K. et al. (2016). Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. *Gastrointest Endosc* 83: 1090–1106.e3.

Landau, M.S., Hastings, S.M., Foxwell, T.J. et al. (2014). Tumor budding is associated with an increased risk of lymph node metastasis and poor prognosis in superficial esophageal adenocarcinoma. *Mod Pathol* 27 (12): 1578–1589. doi: 10.1038/modpathol.2014.66.

Leers, J.M., DeMeester, S.R., Oezcelik, A. et al. (2011). The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. *Ann Surg* 253 (2): 271–278. doi: 10.1097/SLA.0b013e3181fbad42.

Lomo, L.C., Blount, P.L., Sanchez, C.A. et al. (2006). Crypt dysplasia with surface maturation: a clinical, pathologic, and molecular study of a Barrett's esophagus cohort. *Am J Surg Pathol* 30 (4): 423–435. doi: 10.1097/00000478-200604000-00001.

Madhusudhan, C., Saluja, S.S., Pal, S. et al. (2009). Palliative stenting for relief of dysphagia in patients with inoperable esophageal cancer: impact on quality of life. *Dis Esophagus* 22: 331–336.

Mahajan, D., Bennett, A., Liu, X. et al. (2010). Grading of gastric foveolar-type dysplasia in Barrett's esophagus. *Mod Pathol* 23: 1–11. doi.org/10.1038/modpathol.2009.147.

Manner, H., May, A., Pech, O. et al. (2008). Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. *Am J Gastroenterol* 103: 2589–2597.

Maple, J.T., Abu Dayyeh, B.K., Chauhan, S.S. et al. (2015). Endoscopic submucosal dissection. *Gastrointest Endosc* 81: 1311–1325.

Montgomery, E., Bronner, M.P., Goldblum J.R. et al. (2001). Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol* 32 (4): 368–378. doi: 10.1053/hupa.2001.23510.

Motomura D, Chung W, and Bechara R. (2021). Endoscopic therapy for T1b esophageal cancer. *Gastrointest Endosc* 93 (1): 282–283. doi: 10.1016/j.gie.2020.07.065.

Naini, B.V., Souza, R.F., and Odze, R.D. (2016 May). Barrett's Esophagus: A comprehensive and contemporary review for pathologists. *Am J Surg Pathol* 40 (5): p e45–e66. doi: 10.1097/PAS.0000000000000598.

Odze, R.D. (2006). Diagnosis and grading of dysplasia in Barrett's oesophagus. *J Clin Pathol* 59 (10): 1029–1038. doi: 10.1136/jcp.2005.035337.

Phoa, K.N., Pouw, R.E., Bisschops, R. et al. (2016). Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). *Gut* 65: 555.

Prasad, G.A., Buttar, N.S., Wongkeesong, L.M. et al. (2007). Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. *Am J Gastroenterol* 102 (11): 2380–2386. doi: 10.1111/j.1572-0241.2007.01419.x.

Phoa, K.N., Van Vilsteren, F.G., Weusten, B.L. et al. (2014). Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA* 311: 1209–1217.

Qumseya, B., Sultan, S., Bain, P. et al. (2019). ASGE guideline on screening and surveillance of Barrett's esophagus. *Gastrointest Endosc* 90: 335–359.e2.

Rice, T.W., Patil, D.T., and Blackstone, E.H. (2017). 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* 6: 119–130.

Ripley, R.T., Sarkaria, I.S., Grosser, R. et al. (2016). Pretreatment Dysphagia in Esophageal cancer patients may eliminate the need for staging by endoscopic ultrasonography. *Ann Thorac Surg* 101: 226–230.

Sami, S.S., Iyer, P.G., Pophali, P. et al. (2019a). Acceptability, accuracy, and safety of disposable transnasal capsule endoscopy for Barrett's Esophagus screening. *Clin Gastroenterol Hepatol* 17: 638–646.e1.

Sami, S.S., Ravindran, A., Kahn, A. et al. (2019b). Timeline and location of recurrence following successful ablation in Barrett's oesophagus: an international multicentre study. *Gut* 68: 1379–1385.

Sanchez-Vega, F., Mina, M., Armenia, J. et al. (2018). Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell* 173 (2): 321–337.e10. doi: 10.1016/j.cell.2018.03.035.

Sawas, T., Alsawas, M., Bazerbachi, F. et al. (2019). Persistent intestinal metaplasia after endoscopic eradication therapy of neoplastic Barrett's esophagus increases the risk of dysplasia recurrence: meta-analysis. *Gastrointest Endosc* 89: 913–925.e6.

Shaheen, N.J., Falk, G.W., Iyer, P.G., Gerson L.B., and American College of Gastroenterology. (2016). ACG Clinical guideline: diagnosis and management of Barrett's Esophagus. [published correction appears in Am J Gastroenterol. Jul;111(7):1077]. *Am J Gastroenterol* 111 (1): 30–51. doi: 10.1038/ajg.2015.322.

Shaheen, N.J., Falk, G.W., Iyer, P.G. et al. (2022). Diagnosis and management of Barrett's Esophagus: an updated ACG guideline. *Am J Gastroenterol.* 117(4): 559–587. doi: 10.14309/ajg.0000000000001680. PMID: 35354777; PMCID: PMC10259184.

Shaheen, N.J., Sharma, P., Overholt, B.F. et al. (2009). Radiofrequency ablation in Barrett's esophagus with dysplasia. *New Engl J Med* 360: 2277–2288.

Siegel, R.L., Miller, K.D., Fuchs, H.E., and Jemal, A. (2022). Cancer statistics, 2022. *CA Cancer J Clin* 72: 7–33.

Siewert, J.R., Feith, M., Werner, M., and Stein, H.J. (2000). Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 232 (3): 353–361. doi: 10.1097/00000658-200009000-00007.

Singh, S., Sedlack, R.E., and Cook, D.A. (2014). Effects of simulation-based training in gastrointestinal endoscopy: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 12 (10): 1611–1623.e4. doi: 10.1016/j.cgh.2014.01.037.

Stachler, M.D., Taylor-Weiner, A., Peng, S. et al. (2015). Paired exome analysis of Barrett's esophagus and adenocarcinoma. *Nat Genet* 47: 1047–1055.

Sung, H., Ferlay, J., Siegel, R.L. et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality Worldwide for 36 cancers in 185 Countries. *CA: A Cancer J Clinic* 71: 209–249.

Terheggen, G., Horn, E.M., Vieth, M. et al. (2017). A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. *Gut* 66: 783.

Then, E.O., Lopez, M., Saleem, S. et al. (2020). Esophageal cancer: an updated surveillance epidemiology and end results database analysis. *World J Oncol* 11: 55–64.

van Munster, S., Nieuwenhuis, E., Weusten, B. et al. (2021). Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. *Gut* 71 (2): 265–276.

Vieth, M. and Stolte, M. (2005). Pathology of early upper GI cancers. *Best Pract Res Clin Gastroenterol* 19 (6): 857–869. doi: 10.1016/j.bpg.2005.02.008.

Visrodia, K., Singh, S., Krishnamoorthi, R. et al. (2016). Magnitude of missed esophageal adenocarcinoma after Barrett's Esophagus diagnosis: a systematic review and meta-analysis. *Gastroenterology* 150: 599–607e7.

Visrodia, K., Zakko, L., Singh, S. et al. (2018). Cryotherapy for persistent Barrett's esophagus after radiofrequency ablation: a systematic review and meta-analysis. *Gastrointest Endosc* 87: 1396–1404.e1.

Visrodia, K., Zakko, L., and Wang, K.K. (2017). Radiofrequency ablation of Barrett's Esophagus: efficacy, complications, and durability. *Gastrointest Endosc Clin N Am* 27: 491–501.

Wolfson, P., Ho, K.M.A., Wilson, A. et al. (2022). Endoscopic eradication therapy for Barrett's Esophagus related neoplasia. A final 10 year report from the United Kingdom National Halo radiofrequency ablation registry. *Gastrointest Endosc* 96 (2): 223–233.

Yang, D., Perbtani, Y.B., Wang, Y. et al. (2021). Evaluating learning curves and competence in colorectal EMR among advanced endoscopy fellows: a pilot multicenter prospective trial using cumulative sum analysis. *Gastrointest Endosc* 93: 682–690.e4.

Zhang, X., Ly, E.K., Nithyanand, S. et al. (2020). Learning curve for endoscopic submucosal dissection with an untutored, prevalence-based approach in the United States. *Clin Gastroenterol Hepatol* 18: 580–588.e1.

References for Surgical Section II.

Depypere, L., Lerut, T., Moons, J. et al. (2017 January 1). Isolated local recurrence or solitary solid organ metastasis after esophagectomy for cancer is not the end of the road. *Dis Esophagus* 30 (1): 1–8.

Low, D.E., Kuppusamy, M.K., Alderson, D. et al. (2019 February). Benchmarking complications associated with Esophagectomy. *Ann Surg* 269 (2): 291–298.

Omloo, J.M., Lagarde, S.M., Hulscher, J.B. et al. (2007 December). Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 246 (6): 992–1000.

Schizas, D., Lazaridis, I.I., Moris, D. et al. (2018 March 14). The role of surgical treatment in isolated organ recurrence of esophageal cancer-a systematic review of the literature. *World J Surg Oncol* 16 (1): 55.

Toxopeus, E.L., Talman, S., van der Gaast, A. et al. (2015 March). Induction chemotherapy followed by surgery for advanced oesophageal cancer. *Eur J Surg Oncol* 41 (3): 323–332.

van der Sluis, P.C., van der Horst, S., May, A.M. et al. (2019 Apr). Robot-assisted minimally invasive Thoracolaparoscopic Esophagectomy versus open transthoracic Esophagectomy for resectable Esophageal cancer: a randomized controlled trial. *Ann Surg* 269 (4): 621–630.

van Workum, F., Verstegen, M.H.P., Klarenbeek, B.R. et al. (2021 Jul 1). ICAN collaborative research group. Intrathoracic vs Cervical Anastomosis after totally or hybrid minimally invasive Esophagectomy for Esophageal cancer: a randomized clinical trial. *JAMA Surg* 156 (7): 601–610.

References for Oncological Section III.

Al-Batran, S.E., Homann, N., Pauligk, C. et al. (2019). Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicine for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomized phase 2/3 trial. *Lancet* 393 (10184): 1948–1957 doi: 10.1016/S0140-6736(18)32557-1.

Bang, Y.J., Van Cutsem, E., Feyereislova, A. et al. (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open label, randomized controlled trial. *Lancet* 376 (9742): 687–697.

Chan, K.K.W., Saluja, R., Delos Santos, K. et al. (2018). Neoadjuvant treatments for locally advanced, resectable esophageal cancer: a network meta-analysis. *Int J Cancer* 143 (2): 430.

Chao, J., Fuchs, C.S., Shitara, K. et al. (2021). Assessment of Pembrolizumab therapy for the treatment of microsatellite instability high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol* 7 (6): 895.

Cunningham, D., Allum, W.H., Stenning, S.P. et al. (2006). Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *NEJM* 355 (1): 11.

Deng, H.Y., Wang, W.P., Wang, Y.C. et al. (2017). Neoadjuvant chemradiotherapy or chemotherapy? A comprehensive systematic review and meta-analysis of the options for neoadjuvant therapy for treating oesophageal cancer. *Eur J Cardiothoracic Surg* 51 (3): 421.

Eyck, B.M., van Lanschot, J.J.B., Hulshof, M.C.C.M. et al. (2021). Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer. The randomized controlled CROSS trial. *J Clin Oncol* 39 (18): 1995.

Fan, N., Wang, Z., Zhou, C. et al. (2021). Comparison of outcomes between neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy in patients with locally advanced esophageal cancer: a network meta-analysis. *EClin Med* 42: 101183.

Fuchs, C.S., Tomasek, J., Yong, C.J. et al. (2014). Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (REGARD). *Lancet* 383 (9911): 31.

Hulscher, J.B., van Sandick, J.W., de Boer, A.G. et al. (2002). Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 347 (21): 1662.

Janjigian, Y.Y., Shitara, A., Moehler, M. et al. (2021). First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-esophageal junction, and oesophageal adenocarcinoma (Checkmate 649): a randomized, open label, phase 3 trial. *Lancet* 398 (10294): 27.

Janmaat, V.T., Steyerberg, E.W., van der Gaast, A. et al. (2017). Palliative chemotherapy and targeted therapies for esophageal and gastro-esophageal junction cancer. *Cochrane Database Syst Rev* 11.

Kelly, R.J., Ajani, J.A., Kuzdal, J. et al. (2021). Adjuvant Nivolumab in resected esophageal or gastroesophageal junction cancer. *N Eng J Med* 384 (13): 1191.

Rice, T.W., Rusch, V.W., Apperson-Hansen, C. et al. (2009). Worldwide esophageal cancer collaboration. *Dis Esophagus* 22 (1): 1.

Shitara, K., Ajani, J.A., Moehler, M. et al. (2022). Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature* 603 (7903): 942.

Shitara, K., Doi, T., Dvorkin, M. et al. (2018). Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS). *Lancet Oncol* 19 (11): 1437.

Shitara, K., Van Cutsem, E., Bang, Y-J. et al. (2020). Efficacy and safety of pembrolizumab plus chemotherapy versus chemotherapy alone for patients with first-line, advanced gastric cancer. The KEYNOTE-062 phase 3 randomized clinical trial. *JAMA oncol* 6 (10): 1571.

Sjoquist, K.M., Burmeister, B.H., Smithers, B.M. et al. (2011). Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 12 (7): 681.

Sun, J.M., Shen, L., Shah, M.A. et al. (2021). Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomized, placebo-controlled phase 3 trial. *Lancet* 398 (10302): 759.

Ter Veer, E., Creemers, A., de Waal, L. et al. (2018). Comparing cytotoxic backbones for first-line trastuzumab containing regimens in human epidermal growth factor receptor 2 positive advanced oesophagogastric cancer: a meta-analysis. *Int J Cancer* 143 (2): 438.

Tomita, Y., Molodvan, M., Chang Lee, R. et al. (2020). Salvage systemic therapy for advanced gastric and oesophago-gastric junction adenocarcinoma. *Cochrane Database Syst Rev* 11: CD012078.

Van Hagen, P., Hulshof, M.C., van Lanschot, J.J. et al. (2012). Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 366 (22): 2074–2084.

Wilke, H., Muro, K., Van Cutsem, E. et al. (2014). Ramucirumab plus paclitaxel versus placebo plus paclitaxel…. (RAINBOW). *Lancet Oncol* 15 (11): 1224–1235.

Zhang, Y. (2013). Epidemiology of esophageal cancer. *World J Gastroenterol* 19: 5598–5606.

5 Esophageal Squamous Cell Carcinoma

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[Aspects of the management of esophageal cancer including biologic and immunotherapy are also covered in Chapter 4].

Section 1 Introduction

Esophageal cancer (EC) is an aggressive disease, as it is the eight-most common cancer and the sixth-most common cause of death worldwide (i.e. 572.000 new cases and 509.000 deaths yearly) (Bray et al. 2018; Gibson 2022). Esophageal cancer can be divided in two main histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. Approximately 70% esophageal cancers occur in men. Incidence and mortality rates differ between sexes worldwide. The geographic variation in esophageal cancer incidence is striking and both histological subtypes have different etiologies. In Western countries, alcohol consumption and smoking are the major risk factors for esophageal squamous cell carcinoma (ESCC). In the East, dietary products high in nitrogenous components (common in Eastern cuisine) and areca nuts (commonly chewed in Southeast Asia) are contributing to the higher incidence as well. Others have also suggested a genetic basis for ESCC. In this chapter, the detection, staging and treatment of ESCC is discussed focusing on new developments in the past 15 years in the western and eastern world.

Section 2 Screening and Surveillance

Screening Techniques

ESCC has a poor prognosis when diagnosis is delayed. Early detection and pre-symptomatic screening may improve outcome of the disease. Recent studies provided insights into early diagnosis of ESCC using advanced endoscopic imaging, cytology, and serum blood-markers.

Endoscopy (Advanced Techniques)

The gold standard diagnostic tool for ESCC and its precursor lesions is esophagogastroduodenoscopy (EGD) with biopsies. This can be time consuming, expensive, unpractical, and has a sensitivity ranging from 28% to 85% for the detection of high-grade dysplasia. (Taylor et al. 2013)

Image Enhanced Endoscopy (IEE)

IEE provides contrast enhancement of mucosal surface and blood vessels without the use of stains or dyes. Selective light transmittance is accomplished by the optical filtering of white light in narrow-band imaging (NBI) and with post-image processing in blue laser imaging (BLI), linked color imaging (LCI) and iScan. NBI is commonly used in the diagnosis and surveillance of esophageal squamous dysplasia (ESD), the precursor lesion to ESCC. A meta-analysis showed per-patient

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and per-lesion sensitivities of 88% and 94%, respectively, in the detection of ESCC using IEE (Morita 2017).

Dye Spray Chromoendoscopy

Dye spray chromoendoscopy involves vital staining by spraying dyes on the luminal surface (i.e., methylene blue, Lugol's iodine solution). Lugol's chromoendoscopy showed a sensitivity per-patient and per-lesion specificities: 92% and 98%, respectively for ESCC (Morita 2017).

Volumetric Laser Endomicroscopy (VLE)

VLE is a relatively novel imaging technology generating a circumferential scan of 6 cm segments of the esophagus to a depth of 3 mm into the mucosal and submucosal layers with 7 μm axial resolution. Although VLE has been mainly applied to Barret's esophagus, the technique may be suitable for screening and surveillance of ESCC due to the long esophageal segments included in the field of view. (Kohli 2017) Further prospective and large sample-size studies are needed to further explore the potentials.

Cytology

Cytology techniques such as esophageal balloon cytology and cytosponge have been studied to detect ESCC and (high-grade) dysplasia in high-risk subjects with predisposition to SCC. Despite its simple design, the low sensitivity – below 50% for dysplasia and cancer – make them less suitable for screening (Wang et al. 2005b).

Serum Biomarkers

Blood biomarkers are ideal for screening programs given its minimal invasiveness. Studies on the immune response to cancer in humans with the presence of autoantibodies against intracellular and surface antigens are in the pipeline. In this regard, antibodies directed against circulating tumor-associated antigens have been demonstrated to be present in the serum of patients many years before the diagnosis of cancer and might be a useful non-invasive tool in cancer screening. Circulating molecules that have shown potential utility include CEA, Cyfra21-1, SCC-Ag, metabolites, proteins, NLR, autoantibodies, and circulating RNAs (circRNAs). Liquid biopsies appear as promising non-invasive inexpensive tests for the diagnosis of EC, but further investigations are required to extensively disclose their clinical utility (Visaggi et al. 2021).

Screening Programs

Effective screening involves a relatively simple, inexpensive test to target a large number of people in order to identify those at risk for EC. Risk factors related to ESCC are for example, smoking, alcohol, dietary products high in nitrogenous components (common in Eastern cuisine), and areca nuts (commonly chewed in Southeast Asia). Others also suggested a genetic or viral (Human papillomavirus) cause as an underlying reason for ESCC development. Genome-wide association studies have shown single nucleotide polymorhpisms (SNPs) for alcohol dehydrogenases 1B (rs1229984), aldehyde dehydrogenase 2 family (rs671) and a region of chromosome 20 (C20orf54). Screening programs should be designed to effectively recognize high-risk patients (Arnal et al. 2015).

Although good screening programs enable cancer prevention, such programs are not cost-effective in most parts of the world due to the low incidence of ESCC especially in Western countries. Since the 1970s, several screening methods have been developed and tested in China, including balloon cytology with smears, liquid-based balloon cytology and/or occult blood detection. The Cancer Screening Program in Rural Areas is a massive screening method on EC and gastric cancer in high-risk areas in China. Residents of communities with high rates of ESCC aged 40–69 were screened once by endoscopy with Lugol's iodine staining. There was a significant reduction in cumulative mortality in the screening group (3.35 vs 5.05%) and a significantly lower cumulative incidence of ESCC (4.17% vs 5.92%; $p<0.001$) (Wang et al. 2005a).

Costs and effectiveness of 12 different screening methods were compared, and two endoscopic strategies demonstrated cost-effectiveness. In low-income level areas with limited health-care access, one screening endoscopy at age 50 years was recommended, with 5-year follow-up for low-grade dysplasia and 3-year follow-up for high-grade dysplasia. In areas with higher incomes and better health care access, three screening endoscopies with 5-year intervals starting at the age of 40 years were recommended with same monitoring strategies of low-grade and high-grade dysplasia (Chen 2021).

Besides China, other screening programs are limited to testing for trials and have not been implemented in guidelines. Countries such as Japan, Taiwan, and Iran are working toward a cost-effective screening strategy.

Summary

1. Advanced endoscopic imaging such as image enhanced endoscopy, dye spray chromoendoscopy, and volumetric laser endomicroscopy have shown promising results with higher sensitivity in the detection of early cancerous lesions.
2. Cytology and serum blood-markers appear as promising non-invasive test, but further investigations are required to assess clinical utility.
3. Existing screening programs are limited to endoscopic screening in high-risk Chinese populations. A cost-effective screening strategy for ESCC for high-risk areas should be implemented.

Section 3 Clinical Presentation/ Diagnosis

Clinical Presentation/Diagnosis

Esophageal squamous cell carcinoma frequently presents in the middle or proximal esophagus. Despite different histology, patients with both adenocarcinoma and ESCC located in the thoracic part of the esophagus have similar clinical presentation. Only a minority group of patients (6–10%) is asymptomatic at the time of diagnosis (Cavallin 2018).

Signs and Symptoms

At an early stage of the disease, symptoms can be non-specific such as minor change in sensation when swallowing or dyspepsia. When the tumor progresses, this is usually followed by impairment of the ability to swallow (dysphagia) and/or pain on swallowing (odynophagia). Meat and bread are often the first type of foods that give to dysphagia or regurgitation, often progressing over weeks to dysphagia for semi-solids and liquids. Some patients present with dribbling saliva (sialorrhea), when even water cannot be swallowed.

Patients with locally advanced tumors often present with weight loss caused by dysphagia, which occurs if the tumor causes reduction of the esophageal diameter. Also cancer-related anorexia may contribute to weight loss. Patients can experience pain in the epigastric or retrosternal area. Pain in other body parts, such as bone structures, may indicate metastatic disease.

Some patients have obscure gastro-intestinal blood loss as a sign of underlying ESCC, which can result in iron deficiency anemia (Schatz and Rockey 2017). Melena or hematemesis can occur especially in patients that take NSAIDs or oral anticoagulants. Acute severe gastro-intestinal bleeding due to tumor invasion into the aorta or pulmonary arteries is rare.

Respiratory symptoms, such as persistent cough and recurrent pneumonia, can be caused by aspiration of undigested food or direct invasion of the tumor in the tracheobronchial three (tracheobronchial fistula) which is a late phenomenon of tumor progression. A small number of patients will present with chest infection or a lung abscess.

Section 4 Clinical Staging

Clinical Staging

Clinical staging is performed to estimate the extent of the disease and to decide which treatment is indicated. Two staging classification systems are commonly used. The 8th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM cancer staging and the Japanese Classification of esophageal cancer (JES) (Kitagawa 2019; Rice 2017). There are some differences between the two staging systems. UICC defines the N-category according to the number of the metastatic regional lymph nodes only and supraclavicular nodes are excluded (Udagawa and Ueno 2018). In JES system, regional nodes are divided into five different patterns according to the primary tumor location, and supraclavicular nodes are defined as regional nodes for thoracic esophageal cancer (Table 2 and Figure 1). The most commonly used staging groups according to the 8th edition of the AJCC/UICC are illustrated in Table 1.

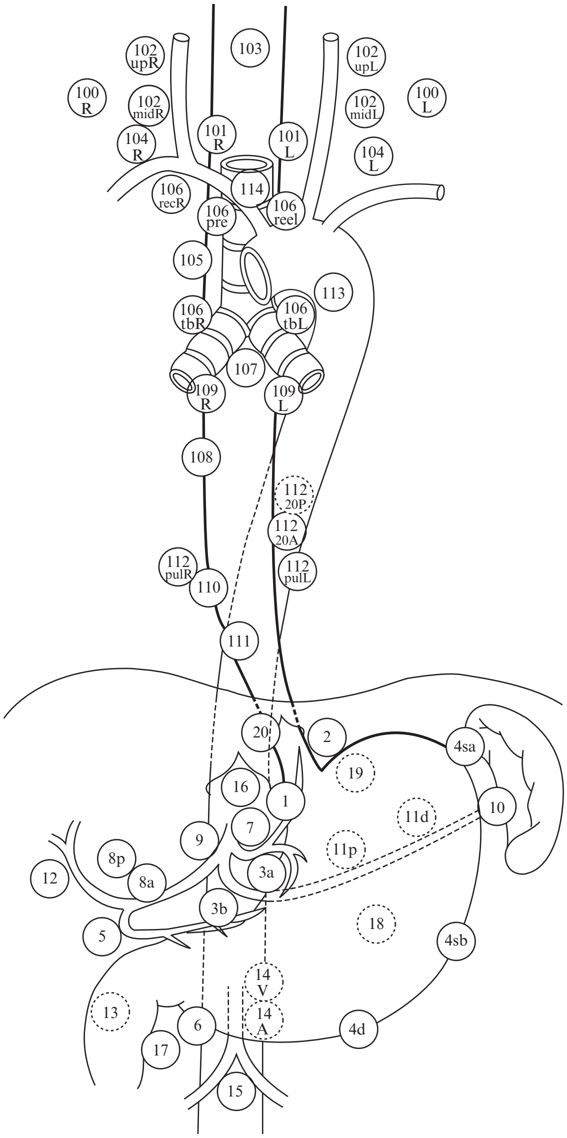


Figure 1 Station numbers of regional lymph nodes.

Table 1 Cancer staging categories for ESCC (Adapted from Rice et al. 2017).

Category	Criteria
T category	T category
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
Tis	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a*	Tumor invades the lamina propria or muscularis mucosae
T1b*	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a*	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b*	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis

Table 2 Lymph node groups according to tumor location (JES classification).

Category	Criteria
T category	T category
TX	Depth of tumor invasion cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor invades mucosa
T1a-EP	Carcinoma in situ (Tis)
T1a-LPM	Tumor invades lamina propria/mucosae
T1a-MM	Tumor invades muscularis mucosae
T1b	Tumor invades submucosa (SM)
T1b-SM1	Tumor invades the upper third of the submucosal layer
T1b-SM2	Tumor invades the middle third of the submucosal layer
T1b-SM3	Tumor invades the lower third of the submucosal layer
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, nerve
T4b	Aorta (great artery), trachea, bronchus, pulmonary vein, pulmonary artery, vertebral body

(Continued)

Table 2 (Continued)

N category

Tumor location	Group 1 (N1)	Group 2 (N2)	Group 3 (N3)
Cervical Ce	101, 106rec[a]	102, 104, 105[a]	100
Upper thoracic Ut	101, 105, 106rec	104, 106tbL, 107, 108, 109	102mid, 106pre, 106tbR, 110, 112aoA, 112pul, 1, 2, 3a, 7, 20
Middle thoracic Mt	106rec, 108, 1, 2, 3a	101, 104, 105, 107, 109, 110, 112aoA, 112pul, 7, 9, 20	106tbL
Lower thoracic Lt	110, 1, 2, 3a, 7, 20	101, 106rec, 107, 108, 109, 112aoA, 112pul, 9	104, 105, 106tbL, 111, 8a, 11p
Abdominal Ae	110, 1, 2, 3a, 7, 20	111, 112aoA, 112pul, 8a, 9, 11p, 19	106rec, 107, 108, 109, 11d

Nodes other than N1 through N3 are expressed as N4

[a] Limited to the area which can be dissected from the cervical incision

M category

Mx	Distant organ metastasis cannot be assessed
M0	No distant organ metastasis
M1	Distant organ metastasis

Routine Clinical Staging

Since 2017, esophagogastroduodenoscopy (EGD) with biopsies, endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) of suspected lymph nodes and ^{18}F-FDG positron emission tomography/computed tomography (FDG-PET/CT) are mainstays in clinical staging of esophageal cancer or cancer of the esophagogastric junction (EGJ) (Rice 2017). This is in accordance with the National Comprehensive Cancer Network (NCCN) guideline (Ajani 2019). The order in which these diagnostic modalities are used can vary, depending on physician preference, costs, and availability. In general, there are two common strategies. The first consists of EGD with biopsies, EUS, and EUS-FNA to determine clinical T- and N-stage followed by FDG-PET/CT for additional clinical N-stage and detection of distant metastases (M-stage). This strategy is efficient because all clinical staging categories are determined, but is also costly. An endoscopic submucosal dissection (ESD) can be performed for an early cancer when no (lymph node) metastases are present. The second strategy begins with FDG-PET/CT to determine clinical M-stage and therefore in case of cM1 stage it can be considered that no additional diagnostics are required. This second strategy is cost-effective, but, does not cover the entire TNM-stage.

Endoscopy with Biopsy

In the developed world esophageal cancer is usually diagnosed at upper endoscopy with biopsy. Occasionally a barium swallow is the first investigation but it must be followed by endoscopic biopsy to confirm the diagnosis when abnormalities are seen. During endoscopy, anatomical landmarks are mapped, as well as the location – for ESCC often proximal or mid esophagus – and circumferential extent of the tumor (Rustgi and El-Serag 2014). These landmarks are the distance from the incisors to the upper esophageal sphincter, the upper and lower border of the tumor, the location of the Z-line, gastric folds, and diaphragm. Biopsies are taken from all suspected areas to confirm pathological diagnosis of ESCC.

Computed Tomography (CT)

CT should include the neck, thorax, and abdomen, and be performed with oral and intravenous contrast agents to evaluate N- and M-stage. With the advent of multi-detector CT, more accurate staging of esophageal cancer is possible (Kim et al. 2009). The high definition of scans now also allows more accurate primary tumor and nodal staging, although these parameters may be more accurately defined by endoscopic ultrasound.

Endoscopic Ultrasound (EUS)

Endoscopic ultrasound is considered to be the best tool to distinguish T1 lesions from T2-T4 lesions and for estimating the depth of ESCC invasion into the esophageal wall with a high sensitivity and specificity of 81–92% and 94–97%, respectively (Puli et al. 2008; Quint and Bogot 2008). For cT1 cancers, EUS overestimates the depth of invasion in 20–30% of patients (Gotink 2017). In these patients, endoscopic judgment is the mainstay to assess if a cT1 esophageal cancer may be endoscopic resectable. EUS uses high-resolution probes which provides multi-layered echo structures of the esophageal wall. Linear EUS with FNA of suspected lymph nodes on indication should be carried out to evaluate lymph node involvement. Accurate staging of the primary tumor and locoregional lymph nodes by EUS can be used to inform decisions on curative therapy, including primary chemoradiotherapy, neoadjuvant therapy followed by surgery or surgery alone. Despite the high accuracy of EUS for ESCC staging, lymph node metastasis in the neck or abdominal field are difficult to detect by EUS and thus a PET/CT of the neck should be performed.

Positron Emission Tomography/Computed Tomography (PET/CT)

Positron emission tomography (PET) is a unique imaging modality using the radiopharmaceutical ^{18}F-FDG (2[^{18}F]-fluoro-2-deoxy-D-glucose) for the detection of high rate glucose metabolism within carcinomas. FDG-PET in esophageal cancer plays an important role in clinical staging (detection of suspicious lymph nodes, distant metastasis) but is also of value as diagnostic evaluation modality after (chemo)radiotherapy or in early detection of recurrent disease (surveillance).

PET/CT has great advantage as not only FDG uptake but also tumor size by CT part could be measured simultaneously. The detection rate of esophageal cancer (i.e. FDG uptake) is 0% in pT1a where the tumor confined in the mucosal layer, and 20% in pT1b up to the submucosal layer, and 100% when depth reached pT2 or more (Kato 2005). Also, PET/CT shows additional value, as it improves specificity over morphological image to assess locoregional lymph node metastases (Miyazaki 2014; Van Westreenen et al. 2004). Where microscopic metastasis sometimes causes false negative results, inflammatory diseases such as pneumonia and sarcoidosis could explain false positive results as well as esophagitis at the level of the primary tumor. In these circumstances, shape and size of lymph nodes are helpful to distinguish infection from lymphadenopathy due to cancer involvement. Finally, PET/CT is particularly useful in advanced cancer with high possibility of distant metastases, since high contrast of PET enables to detect lesions that are missed by CT-scan. In case brain metastases are suspected based on clinical symptoms, an MRI is essential to exclude or diagnose brain metastases, but is not part of standard staging.

Other Staging Techniques

In addition to the diagnostic modalities already described, a variety of specific diagnostic and imaging modalities may be recommended by the multidisciplinary tumor board (MTB) for tumor staging depending on the presentation, site of the primary tumor or suspicion of metastatic disease.

Bronchoscopy

The proximal part of the intrathoracic esophagus is located between the trachea and the vertebral column. When esophageal cancer is located beyond the level of the carina, tracheobronchial invasion (T4b) may be present which often is associated with palliative care. Because of the therapeutic consequences of tracheobronchial invasion, patients with these proximal esophageal tumors should therefore undergo pretreatment bronchoscopy (with biopsy on indication) when CT-scan or EUS suggests airway invasion (Allum 2002; Omloo 2008). Other studies even suggest to include bronchoscopy as routine diagnostic modality for esophageal tumors located at or above the level of the carina, because of the high incidence of airway involvement (Carreiro 2013; Riedel 2000).

Endobronchial Ultrasonography (EBUS)

During endobronchial ultrasonography a radial probe or balloon-probe is passed through the working channel of the bronchoscope. While the balloon probe requires inflation of the balloon for ultrasonographic visualization, the radial probe requires direct apposition to the airway wall. Endobronchial ultrasonography allows the pulmonologist take fine needle aspirations of lymph nodes not accessible with EUS or to take biopsies from lesions suspicious or tumor infiltration in the trachea. Finally, EBUS could also improve tumor staging, by determining the depth and extent of tumor into the tracheobronchial wall.

MRI-scan

Magnetic resonance imaging (MRI) is a non-irradiating and non-invasive promising technique because it provides excellent soft-tissue contrast which allows us to better assess morphological differences between the normal and pathologic esophagus. Nevertheless, MRI does not have a role in routine clinical staging yet because of its low availability and technical limitations (e.g. motion artifacts). Some studies on high-resolution T2-weighted and diffusion-weighted MRI showed that MRI could clearly depict the different layers of the esophageal wall (Wei 2017; Yamada 2014). The T2-weighted technique showed high accuracy to distinguish tumor stage T2 and T3, but it tends to over stage T1 tumors. A recent meta-analysis of 11 trials showed a pooled sensitivity of 92% (95% CI 82–96) and specificity of 67% (95% CI 51–81) for MRI used to distinguish T0 and T1 tumor stages, and sensitivity and specificity of respectively 86% (95% CI 76–92) and 86% (95% CI 75–93) for differentiation between T2 or lower disease and T3 and higher disease (Lee 2021). Recent studies focused on the performance of MRI for lymph node assessment showed pooled sensitivity of 71% (95% CI 60–80) and specificity of 72% (95% CI 64–79). To conclude, MRI has a good sensitivity for T-staging in esophageal cancer and to discriminate between metastatic and non-metastatic lymph nodes, which is promising for the future role of MRI in routine clinical staging.

Diagnostic Laparoscopy

Most staging algorithms also include laparoscopy in the assessment of tumors of the distal esophagus. Laparoscopy could provide more accurate information about local invasion of the tumor, lymph node metastases and distant metastases and allows the surgeon to take biopsies of small peritoneal or liver surface metastases which may not be apparent on PET/CT. It also allows direct anesthetic assessment of patients who may be recommended to have surgical resection as part of definitive treatment. Similarly, staging thoracoscopy and mediastinoscopy are sometimes recommended.

Summary

1. The 8th edition of UICC/AJCC TNM and the Japanese classification system JES are commonly used to stage esophageal cancer.
2. Routine clinical staging consists of upper endoscopy with biopsies, endoscopic ultrasonography with fine-needle aspiration and ^{18}F-FDG PET/CT.
3. Depending on clinical presentation, site of the primary tumor or clinical suspicion, additional tests including bronchoscopy, EBUS, MRI-scan or diagnostic laparoscopy/thoracoscopy may be indicated.

Section 5 Histopathological Staging

Handling of Specimens

Accurate pathological staging requires careful examination of the gross specimen for cancer location, size, configuration, margins, invasion depth, and nodal status.

1. Endoscopic Resection Specimen

Endoscopic submucosal dissection (ESD) has been recognized as a modality for both diagnosis and treatment of early-stage ESCC. (Kumarasinghe 2020; Marginean 2020). Compared to endoscopic mucosal resection, ESD provides larger and intact specimens with submucosal tissue for accurate pathological assessment of tumor grade, invasion depth and lymphovascular invasion. Specimens should be pinned out on a board in order to avoid the intern tendency to curl and fixed in 10% buffered formalin (for half a day or more often overnight). According to the guideline of Japan Esophageal Society (JES), the esophageal mucosa can be treated with a relatively low concentration (0.1–0.5%) of iodine solution to increase the contrast between lesions and normal areas. (Japanese Esopahgeal Society 2017) After inking the margins, the specimen should be serially cut in a 2- to 4-mm interval and entirely submitted for pathological assessment.

2. Esophagectomy Specimen

Patients with ESCC are often treated with chemotherapy and radiation therapy prior to resection. The main tumor mass may be absent with only a shallow ulcer, mucosal erosion, or depressed fibrotic lesion at its former site. The specimen should be opened longitudinally, preferably form the left side, with the size of esophagus and stomach measured and recorded. The size of any identified lesion and its distance to margins should be recorded. After inking the margins, the specimen should be pinned out on a board and fixed in 10% buffered formalin overnight. A superficial lesion should be serially cut longitudinally and entirely submitted for pathological sections. For an advanced lesion, representative sections including one with the deepest invasion should be taken. Surgical margins should be evaluated both macroscopically and microscopically. Lymph nodes submitted as separate specimens should also be documented in the pathology report.

Esophageal Dysplasia

The precursor of ESCC is dysplasia of squamous epithelium. Unlike invasive carcinoma, disoriented proliferation of epithelial cells in squamous dysplasia is limited to the basal membrane. On white-light endoscopy, neoplastic disease appears as a flat, slightly depressed lesion with mild redness. In pathological sections, squamous dysplasia displays both cytological atypia and architectural distortion. Cytological atypia is characterized by nuclear abnormalities, including enlargement, pleomorphism, hyperchromasia, loss of polarity, and overlapping. Architectural distortion is characterized by impaired epithelial maturation.

The grading system for squamous dysplasia has been controversial throughout the years and different systems were used in Eastern and Western practices. Since 2000, the WHO introduced a two-tier system (low-grade vs. high-grade dysplasia). This has been the sole recommended classification system by the WHO Classification in 2019. (WHO Editorial Board 2019) The term “squamous cell carcinoma in situ” frequently used in Japan and some other parts of Asia has been classified as “high-grade dysplasia,” when more than half of the epithelium is involved or when severe cytological atypia is present (regardless of the extent of epithelial involvement) (Figure 2a). Low grade is defined as dysplasia with mild cytological atypia, involving only half of the epithelium (Figure 2b).

Esophageal Squamous Cell Carcinoma

Invasive ESCC is defined as invasion of neoplastic squamous cells through the basal membrane into the lamina propria and deeper layers. When better differentiated, it is associated with keratinization. Macroscopically, it often presents at an advanced pathological stage with an ulcerative mass. A macroscopic classification has been provided by the JES (Japanese Esopahgeal Society 2017).

ESCC is graded by the degree of cytological atypia, mitotic activity and the presence of keratinization. A three-tiered system

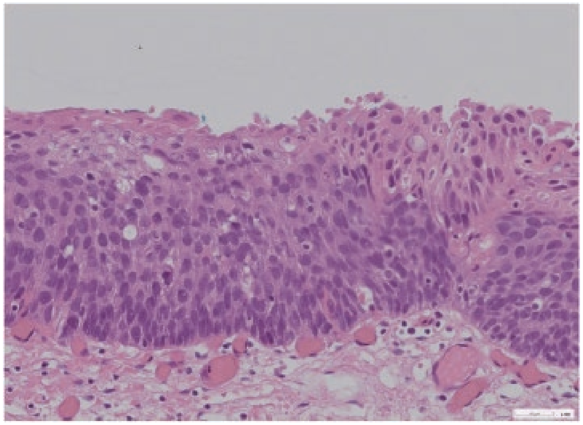


Figure 2a High-grade squamous dysplasia.

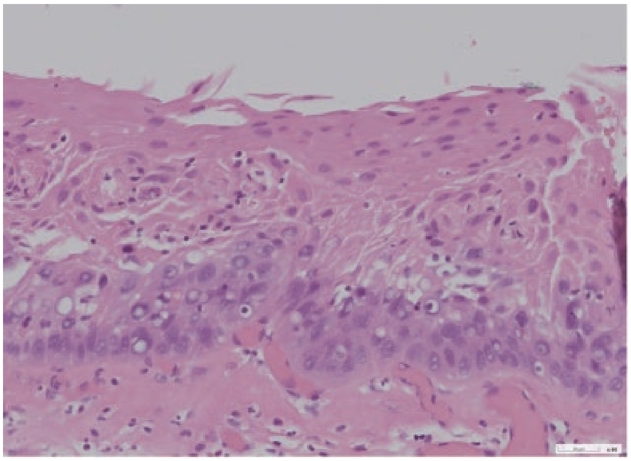


Figure 2b Low-grade squamous dysplasia.

consisting well, moderately or poorly differentiated SCC is commonly applied. However, since the distinction between "well" and "moderately" is highly observer dependent, a two-tiered system (well, moderately vs poorly) may be clinically more relevant.

1 Well differentiated (Figure 3a) = Grade 1: enlarged cells with eosinophilic cytoplasm, intercellular bridges, and keratin pearls formation. Cytological atypia is minimal and the mitotic rate is low. The invasive margin is pushing and the cells remain well ordered.

2 Moderately differentiated (Figure 3b) = Grade 2: more disorganized cells with evident cytological atypia. Mitotic figures are easily identified. There is usually surface parakeratosis, but keratin pearl formation is infrequent.

3 Poorly differentiated (Figure 3c) = Grade 3: predominantly basal-like cells forming nests, which may show central necrosis. The tumor nests consist of sheets or pavement-like arrangements of tumor cells with occasional parakeratotic or keratinizing cells.

Pathological Assessment

There are two different staging systems for ESCC. The most widely accepted system from the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is based on the TNM descriptor published its 8th edition in 2017 (James 2017). In addition to the AJCC system, Japan has its own ESCC staging system (Japanese Esophageal Society 2017). The 8th edition of AJCC/UICC demonstrated that simple sharing of stage groups among classifications was not possible due to marked survival differences and unique pathologic stage groups with (ypTNM) or without preoperative treatment (pTNM). Today, the clinical relevance of pathologic staging remains relevant for early-stage cancers, as the most accurate reflection of cancer facts and as a survival reference point, but depends greatly on neoadjuvant therapy for advanced-stage cancers.

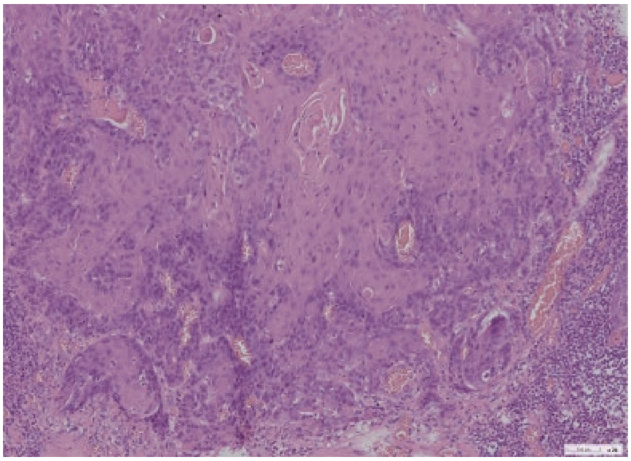


Figure 3a Well-differentiated squamous cell carcinoma of the esophagus.

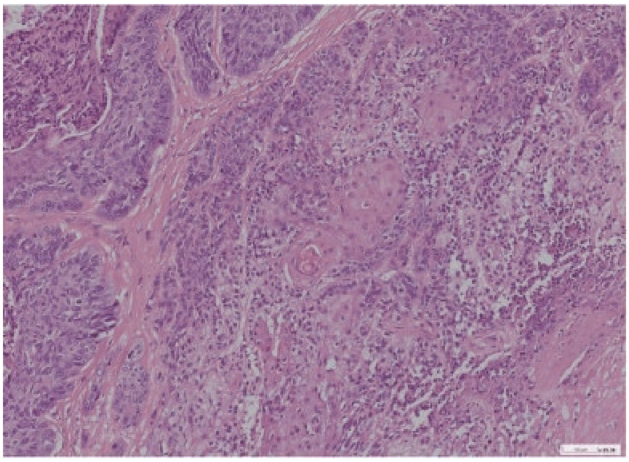


Figure 3b Moderately differentiated squamous cell carcinoma of the esophagus.

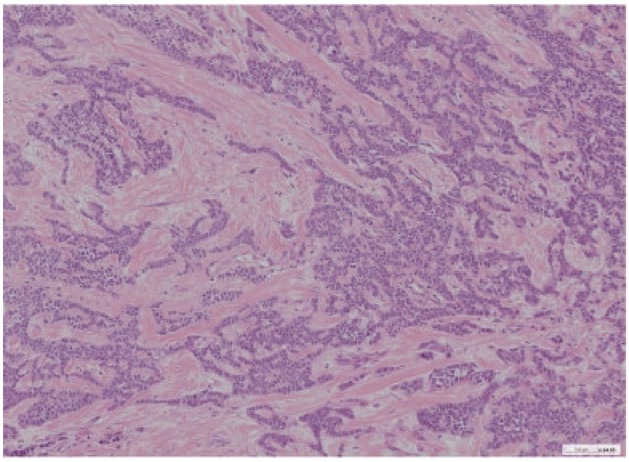


Figure 3c Poorly differentiated squamous cell carcinoma of the esophagus.

Pathological Staging of Squamous Cell Carcinoma

The most commonly used staging groups are the classifications according to the 8th edition of the AJCC/UICC, as illustrated in Table 3. The alternative Japanese staging manual is discussed in the previous section (Table 4 and Figure 1).

Table 3 Pathologic stage groups for ESCC (Adapted from Rice et al. 2017).

pStage group	pT	pN	pM	pGrade	pLocation
0	Tis	N0	M0	N/A	Any
IA	T1a	N0	M0	G1, X	Any
IB	T1b	N0	M0	G1, X	Any
	T1	N0	M0	G2-3	Any
	T2	N0	M0	G1	Any
IIA	T2	N0	M0	G2-3, X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
IIB	T3	N0	M0	G2–3	Upper/middle
	T3	N0	M0	X	Any
	T3	N0	M0	Any	X
	T1	N1	M0	Any	Any
IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
IIIB	T4a	N0-1	M0	Any	Any
	T3	N1	M0	Any	Any
	T2-3	N2	M0	Any	Any
IVa	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	T1-4	N3	M0	Any	Any
IVb	T1-4	N0-3	M1	Any	Any

N/A, not applicable; X, not defined.

Table 4 Morbidity after esophagectomy in cornerstone trials.

	Pulmonary complications	Anastomotic leakage	Laryngeal nerve injury	Postoperative mortality
Open				
MIRO-trial	30%	7%	–	6%
TIME-trial	34%	7%	14%	2%
ROBOT-trial (open thoracotomy)	58%	20%	11%	2%–
Minimally invasive				
Hybrid (MIRO-trial)	18%	11%	\–	4%
MIE (TIME-trial)	12%	12%	2%	3%
Robot-assisted MIE (ROBOT-trial)	32%	24%	9%	9%

Abbreviations: MIE: minimally invasive esophagectomy

Pathological Staging of Superficial Squamous Cell Carcinoma

According to JES, esophageal superficial SCC can be subtyped based on the depth of tumor invasion. The mucosal layer T1a is divided into three layers (T1a-EP, T1a-LPM, and T1a-MM), and the submucosal layer T1b is also divided into three layers (T1b-SM1, T1b-SM2, and T1b-SM3). In endoscopically resected specimens, lesions located in the submucosa within 200 µm of the muscularis mucosae are identified as T1b-SM1, and lesions invading beyond this range are identified as T1b-SM2.

Pathological Staging after Neoadjuvant Therapy

Chemo- and/or radiotherapy is frequently given before surgery and induces changes in both tumor cells and surrounding tissue. While new lesions usually arise from the mucosa, recurrent lesions after chemoradiotherapy could develop in relatively deep areas of the esophagus without concomitant intraepithelial squamous lesions. Endoscopic biopsy of such deep lesions could be challenging.

Epithelial cell changes such as nuclear enlargement or shrinkage, nuclear vacuolation, apoptosis, and necrosis are seen in tumor cells. Dying cells may release keratin and undergo dystrophic calcification and elicit a surrounding giant cell reaction. Other histologic responses to therapy include neutrophilic or chronic inflammation. Stromal changes such as fibrosis and sometimes stromal elastosis could be present and regional vessels typically show intimal proliferation, endarteritis obliterans, telagiectasia, or organizing thrombi. Lymph nodes may show fibrosis, necrosis, calcification and keratin with giant cell reaction. Lymph nodes with these changes, and without any viable cancer cells, should be considered negative for metastasis (ypN0). On the other hand, particularly in the mediastinal lymph nodes, fibrotic changes can occur independently from cytotoxic treatment. Immunohistochemical stains such as -keratin AE1/AE3 may be used to confirm the presence of rare residual cancer cells and. – should be always interpreted in conjunction with morphologic findings.

A tumor regression grade (TRG) is used to classify the extent of tumor regression and is an important prognostic factor. (Figure 4a/b and 5a/b)The first applied method was the Mandard system, graded by comparing the amount of residual tumor versus the amount of therapy-induced fibrosis. (Mandard 1994) Another concept is an estimation of the amount of residual tumor (%) in relation to the tumor bed, where complete regression or < 10% residual tumor is related to a good prognosis. (Becker 2003) The Japanese version proposed by the JES with cutoff value of 1/3 and 2/3 for residual tumor, is also widely used in ESCC (JES 2017). In a Delphi survey that could represent an international standard for histopathologic TRG grading of gastroesophageal carcinomas, the expert panel recommended a four-tiered TRG system for assessing the primary tumor combined with a three-tiered system for grading therapeutic response in metastatic lymph nodes (Saliba 2021):

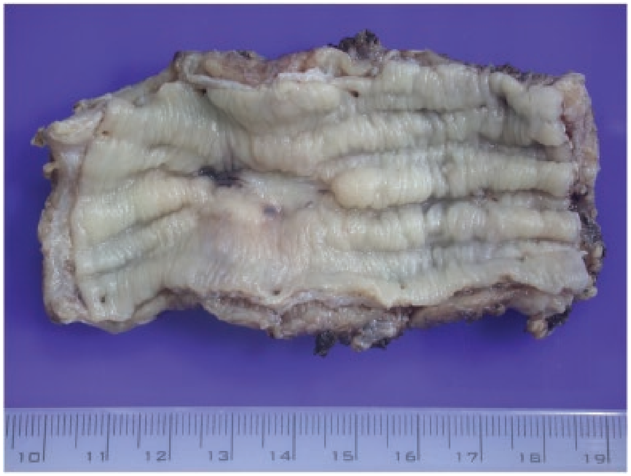


Figure 4a Depressed fibrotic lesion of the esophagus after neoadjuvant chemoradiotherapy without residual tumor visible (complete histopathological tumor regression).

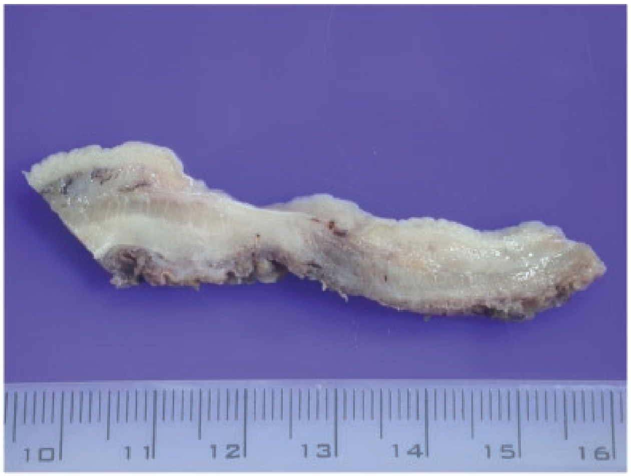


Figure 4b *Cross section of* Figure 4a, *with only fibrosis and no tumor visible.*

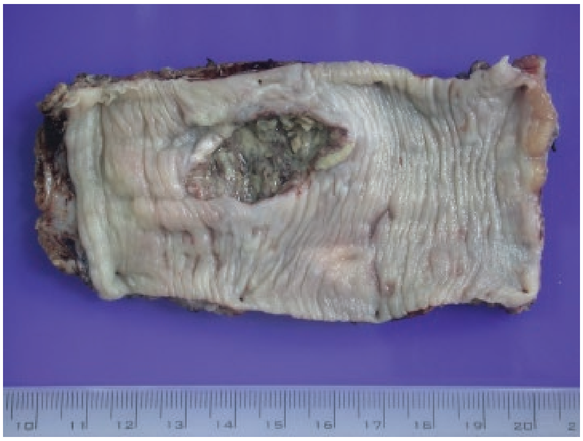


Figure 5a Residual ulcerative tumor of the esophagus after neoadjuvant chemoradiotherapy.

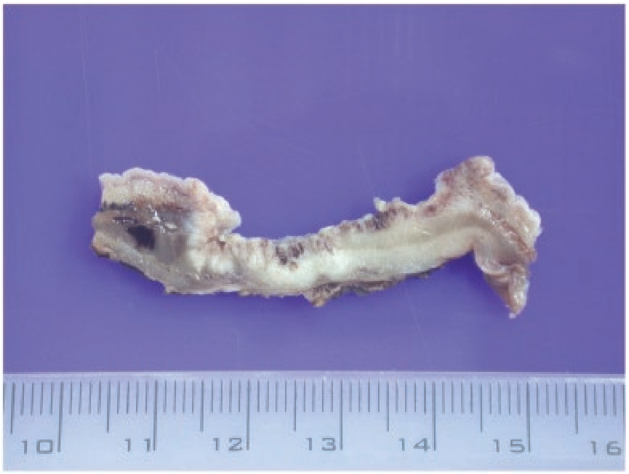


Figure 5b *Cross section of* Figure 4b, *with visible tumor residual.*

1 Tumor: grade 1: No residual tumor (complete histopathologic tumor regression)
2 Tumor: grade 2: less than 10% residual tumor (near-complete regression)
3 Tumor: grade 3: 10–50% residual tumor (partial regression)
4 Tumor: grade 4: greater than 50% residual tumor (minimal/no regression),
5 Lymph node: grade a: no residual tumor (complete histopathologic TRG)
6 Lymph node: grade b: partial regression (tumor cells and regression)
7 Lymph node: grade c: no regression (no sign of tumor response).

Prognostic Values of Pathological Staging Systems

The prognostic values of the pTNM-staging system have been validated extensively in literature for many tumor types treated with surgery alone. The Worldwide Esophageal Cancer Collaboration reported survival discrepancies between different stages of ESCC using data from 33 institutions from 6 continents (Figure 6) (Rice 2016a). New to the eighth edition is stage grouping of patients with ESCC who have undergone neoadjuvant therapy and had pathological review of the resection specimen (Figure 7) (Rice 2017). The pathological stage groups are identical for both adenocarcinoma and SCC (Figure 8) (Rice 2016b).

Summary

1 The 8th edition of UICC/AJCC TNM and the Japanese classification system JES are used for pathological staging of ESCC.
2 The precursor of ESCC is squamous dysplasia and is commonly divided into low- and high- grade dysplasia. ESCC is divided into well, moderately, and poorly differentiated.
3 Compared to the AJCC system, the Japanese classification differs in lymph node mapping as this is based on location of lymph nodes according to tumor location.
4 After neoadjuvant CRT, a tumor regression grade is an important prognostic factor.

Section 6 Curative Treatment Part I

Endoscopic Treatment

For intramucosal esophageal cancers (EC), endoscopic resection (ER) is the standard treatment. The principle of ER is based on the fact that the chance of lymph node metastasis is very small when neoplasia is confined to the mucosal layer of the esophagus, ER can be curative for these tumors. For ESCC invading the muscularis mucosa (T1am3) and those with minimal invasion to the submucosal layer (< 200µm below the muscularis mucosa, T1b), the incidence of lymph node metastasis was 9.3% and 19.6%, respectively (Fujishiro M 2009). The risk of lymph node metastasis of early stage ESCC is also significantly higher compared to adenocarcinoma, thus only selected cases of T1am3 (muscularis mucosae involvement) and T1b are eligible for ER.

The two main types of ER are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Multiple studies showed a higher curative resection rate of ESD than EMR for superficial ESCC and is thereby the most recommended for low- and high-grade intraepithelial neoplasia and superficial mucosal cancer (Noordzij 2019). When performing an ESD, an en-bloc resection with continuous dissection along the submucosal plane is performed.

The rate of complication after ER is discrepant throughout the literature, with acute intra-procedural bleeding ranking from 0.9–24% and perforations from 1.8–6.95%. (Noordzij 2019). One of the main late complications is stricture formation (3.6–49.7%), however most cases can be adequately treated by dilatation. There have been novel insights in the prevention of stricture such as steroid injection therapy and oral steroid administration, tissue shielding methods with polyglycolic acid sheet, autologous oral mucosal epithelial sheet transplantation, and stent placement, but further studies in this research field are needed (Hikichi 2020). Treatment related mortality was 0.2% with a major complication rate of 1.5% in a large series of 1000 EC patients in which ER was performed (Pech 2014).

Although ER is performed with curative intent, curative ER is not always possible. Lesions that are limited to the lamina propria or muscularis mucosae, in the absence of lymphovascular invasion and poor differentiation, don't need additional therapy. Incomplete tumor resection, however, is a criterion for

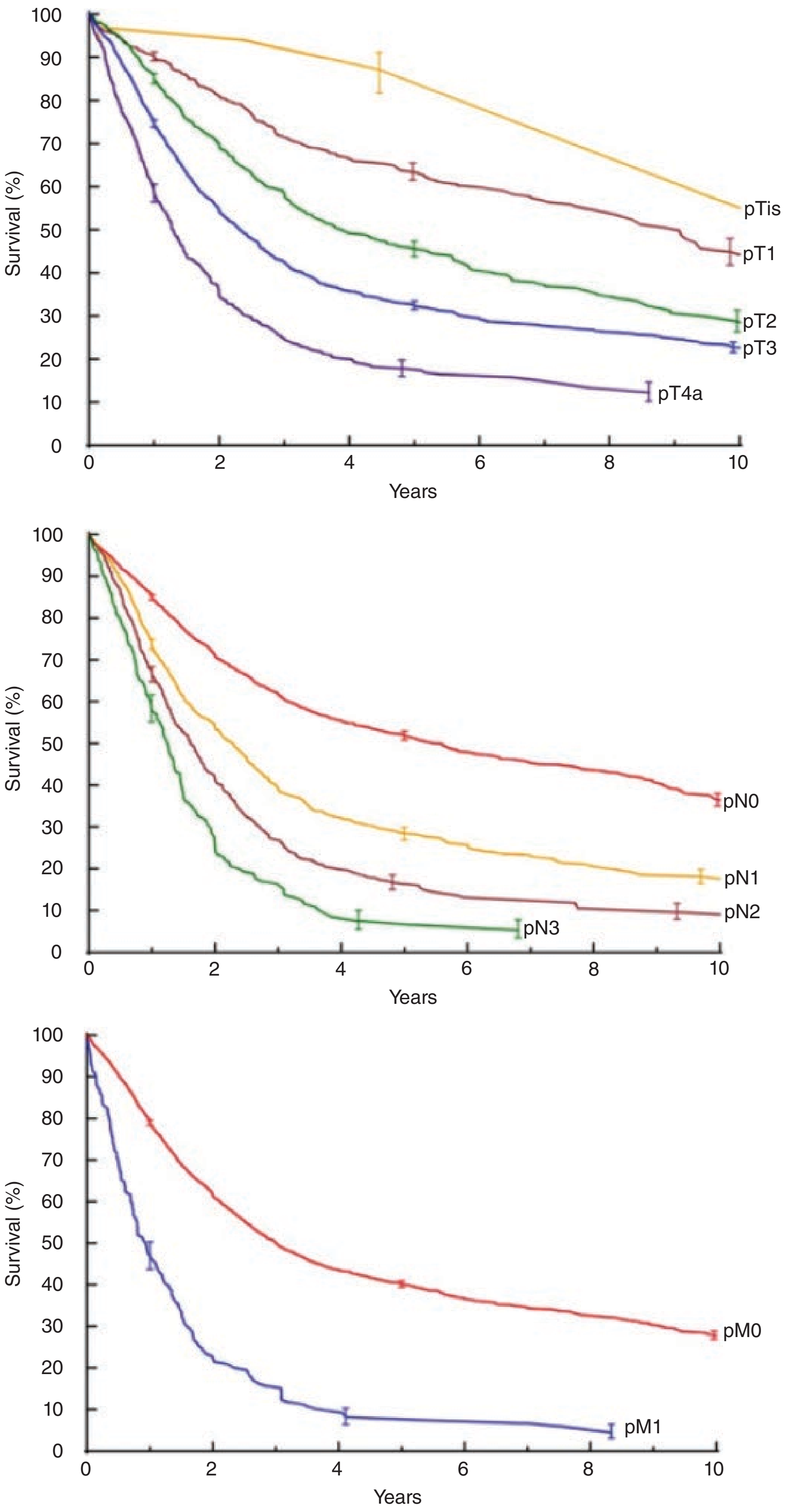


Figure 6 Survival stratified by pT, pN, and pM categories for ESCC.

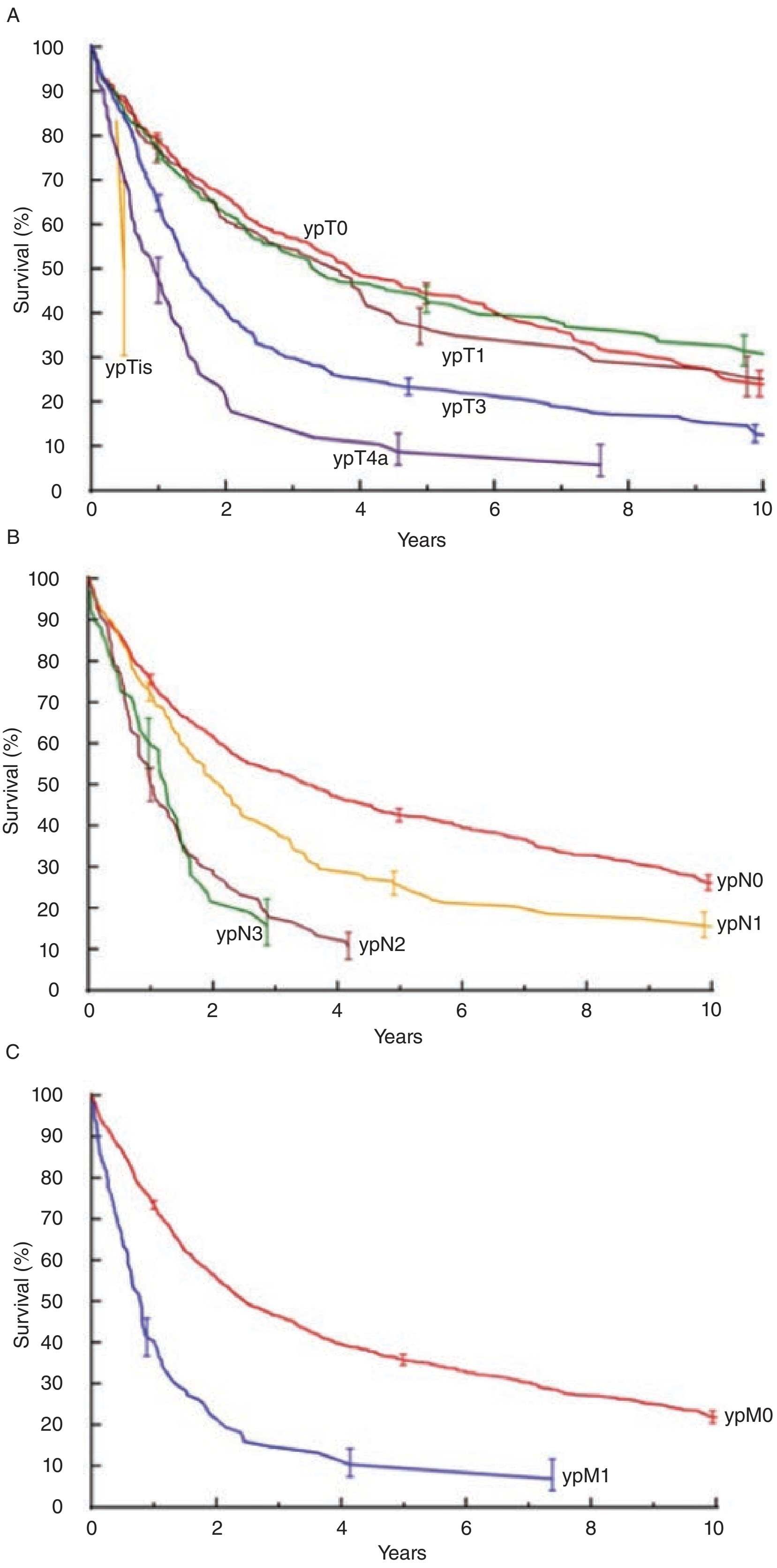
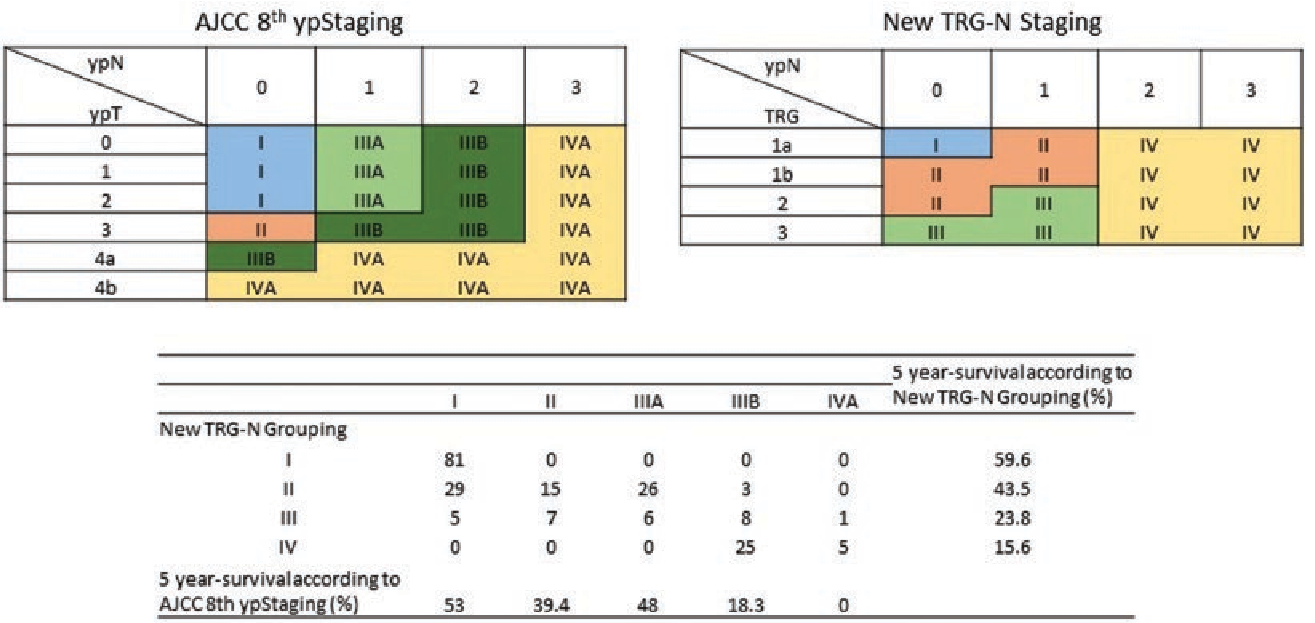


Figure 7 Survival stratified by ypT, ypN, and ypM categories for ESCC.



AJCC 8th ypStaging

ypT \ ypN	0	1	2	3
0	I	IIIA	IIIB	IVA
1	I	IIIA	IIIB	IVA
2	I	IIIA	IIIB	IVA
3	II	IIIB	IIIB	IVA
4a	IIIB	IVA	IVA	IVA
4b	IVA	IVA	IVA	IVA

New TRG-N Staging

TRG \ ypN	0	1	2	3
1a	I	II	IV	IV
1b	II	II	IV	IV
2	II	III	IV	IV
3	III	III	IV	IV

	I	II	IIIA	IIIB	IVA	5 year-survival according to New TRG-N Grouping (%)
New TRG-N Grouping						
I	81	0	0	0	0	59.6
II	29	15	26	3	0	43.5
III	5	7	6	8	1	23.8
IV	0	0	0	25	5	15.6
5 year-survival according to AJCC 8th ypStaging (%)	53	39.4	48	18.3	0	

Figure 8 Postneoadjuvant pathologic stage groups (ypTNM): adenocarcinoma and squamous cell carcinoma.

noncurative ER. While additional esophagectomy is recommended when postoperative histopathological factors indicate a high risk of nodal involvement and/or incomplete resection, accurate patient selection for additional surgery is needed since the majority of additional surgical resections for ESCC were tumor-free compared to adenocarcinoma (Liu 2021).

Another adjuvant therapy for high risk tumors after ER is chemoradiotherapy. The JCOG0508 evaluated the efficacy of CRT after noncurative ER. Three-year progression free survival was 73–88%. Minashi et al. reported that ESD combined with selective adjuvant CRT for cT1bN0M0 ESCC could achieve oncologic results non-inferior to esophagectomy (Minashi 2019). In conclusion, ER is a valuable treatment for superficial ESCC, under the precondition that early stage EC can be accurately diagnosed (Kato 2021).

Ablation

Unlike adenocarcinoma, where several indications for ablation of Barrett's epithelium exist, the role of ablative therapies for ESCC has still to be determined. Endoscopic radiofrequency ablation (RFA) does not allow histological examination and the risk of lymph node metastasis is thus undetermined. RFA is to be combined with other modalities but its' role in the treatment armamentarium for ESCC is still unknown (Noordzij 2019).

Esophagectomy

Radical therapy offers the best chance of control and cure for ESCC and surgical resection still remains the cornerstone of curative treatment.

i Preoperative Selection

Eligibility of a patient for surgical resection strongly depends on the extent of the disease, as well as on the general condition of the patient. Preoperative selection should be carried out carefully. A multidisciplinary team is then necessary for choosing the appropriate treatment for each patient individually, not only on the basis of the TNM-classification system tumor stage, but also depending on tumor location, histological subtype, comorbidities, and age. Patients with T1-2 ESCC without nodal disease are recommended to undergo immediate surgery in Asian practices, but they could also be candidates for preoperative treatment (Ajani 2019). Patients with T3 or N-positive disease are candidates for preoperative chemotherapy and/or radiotherapy followed by elective surgery, while patients with T4a or N3 disease are candidates for definitive chemoradiotherapy followed by salvage surgery. In contrast to adenocarcinoma, ESCC are more proximally located tumors and proximal tumors are usually poor candidates for surgery because of limitations in surgical techniques (e.g., confined working space and poor overview). Furthermore, due to its anatomical proximity to the hypopharynx, surgery includes a combined pharyngo-laryngo-esophagectomy in some cases, resulting in permanent tracheostomy and affecting the quality of life of these patients enormously. These patients frequently depend on definitive chemoradiotherapy, with encouraging three-year outcomes and acceptable toxicity (Borggreve 2018).

As for comorbidities, a large population-based study showed that 65% of the patients have an American Society of Anesthesiologists (ASA) score of 3. Anastomotic leakage is known to be associated with pre-existent cardiovascular disease such as arterial calcifications, making those patients at risk of developing anastomotic leakage due to esophageal conduit necrosis. Preoperative pulmonary function is also related to the incidence of pulmonary complications, but could be reduced by dedicated preoperative physical therapy to increase cardiorespiratory function (Lagarde 2008). Age has historically been a selection criterion for treatment and management in cancer patients, but old age should not be the only reason to exclude patients from receiving survival improving treatments such as surgical resection. The association of age with severity of complications after esophagectomy is demonstrated by an adjusted odds ratio of 1.02 per year increase in age, but no specific limitation of age has been demonstrated as a contraindication for surgery (Nienhueser 2015).

ii Surgical Techniques

Principles of Resection: Tumor Resection

Esophageal tumors tend to spread longitudinally within the submucosa of the esophageal wall. A radical resection without microscopically positive margins (R0 resection) is of great concern for surgeons since it defeats the primary objective of surgery. The definition of a positive radial margin depends on the pathologic reporting system used. The Royal College of Pathologists defines an R1 (microscopically positive) margin as cancer within 1 mm of the margin; the College of American Pathologists defines R1 as microscopic involvement of the margin. Ten percent of esophagectomy patients had positive resection margins and survival is markedly diminished in patients with incompletely resected tumors (Rice 2017).

Principles of Resection: Lymphadenectomy

The lymphatics in the squamous esophagus are located in an extensive, highly interconnected submucosal plexus. They drain through the muscularis propria to a paraesophageal plexus and a group of lymph nodes (LN) situated on the outer wall, then to the periesophageal nodes close by, and finally to lateral esophageal nodes. Sequential drainage may not occur with connections direct from the periesophageal nodes to lateral LN. The Japanese Society published the original and detailed lymph node maps allowing classification and defining radical surgical excision (Akiyama 1994).

A one-field resection would only encompass the para- and periesophageal nodes, a standard two-field resection will include these nodes together with the thoracic duct, the left and right pulmonary hilar nodes, and the paratracheal and tracheal bifurcation nodes. A radical three-field dissection includes the nodes around the right and left recurrent laryngeal nerve, the deep lateral and external cervical chain, and those around the brachiocephalic vein. Lymph node metastasis occurred in 33% of patients with upper thoracic ESCC and 28% in ESCC located in the middle third (Udagawa 2012). In Japan, a three-field LN dissection is recommended, but this is not yet part of the routine surgical practice, especially not in the West due to higher risk on serious postoperative complications. As part of a three-field lymphadenectomy, dissection along the recurrent laryngeal nerve (RLN) could induce RLN palsy and induce aspiration pneumonia, potentially resulting in postoperative deaths (Matsuda 2017).

The Japanese classification of LN is based on the spread of LN rather than the count, which can give additional information on the extent of lymphadenectomy but is more complex to define. (See Section 4: clinical staging) Furthermore, the Japanese classification defines the concepts of D1–D3 dissection, which indicates extent of lymphadenectomy. Using these definitions, a surgeon can plan for extent of dissection based on the location of primary lesions.

1. DX Extent of lymph node dissection cannot be assessed.
2. D0 No or incomplete dissection of Group-1 lymph nodes.
3. D1 Complete dissection of Group-1 lymph nodes, but no or incomplete dissection of Group-2 lymph nodes.
4. D2 Complete dissection of Group-1 and Group-2 lymph nodes, but no or incomplete dissection of Group-3 lymph nodes.
5. D3 Complete dissection of Group-1, Group-2 and Group-3 lymph nodes.

Lymphadenectomy should be based on regional lymph node maps. However, a higher lymph node yield has been associated with improved survival in several international studies but it should be noted that these findings have to be interpreted with caution, and the debate on the benefit of extensive lymphadenectomy has not yet been settled. Lymphadenectomy sufficient to determine pN is different from that necessary for optimal survival; at surgery, a balance of these goals is necessary (Esposito 2020; Visser 2019).

Surgical Approaches

A transthoracic approach is generally considered for esophagectomy to be optimal in oncological terms, as it allows for two-field lymphadenectomy with upper mediastinal dissection. The alternative, transhiatal esophagectomy, was designed to reduce postoperative morbidity and mortality by avoiding thoracotomy and is therefore often reserved for patients with considerable comorbidity and high risk of complications following a potential thoracotomy (Barreto 2010). However, ESCC are mostly located in the upper and middle part of the esophagus, thus operation via the transthoracic route is mostly performed and associated with lower pneumonias, anastomotic leaks, wound infections, strictures, and an improvement in nodal harvest. Survival was also significantly improved in patients who underwent transthoracic esophagectomy (Takahashi 2021).

Anastomotic Techniques

After esophagectomy for cancer removal, gastrointestinal continuity is most commonly restored by gastric tube reconstruction with an esophagogastric anastomosis, but colon- or jejunum-interposition can also be used as alternatives. Several anastomotic techniques are available to construct an esophagogastrostomy. When the lowest part of the thoracic esophagus is resected, an intrathoracic esophagogastric anastomosis high in the chest is performed (Ivor Lewis procedure) (Lewis 1946). If a subtotal esophagectomy is performed, a cervical esophagogastric anastomosis is created (McKeown procedure) (D'Amico 2014). Intrathoracic anastomoses are associated with lower anastomotic leak rates and shorter hospital stay. Reported factors that may explain include less tissue ischemia due to the shorter distance the blood supply must travel and less risk of tension on the anastomosis and further. Some surgeons still prefer a cervical anastomosis, however, because the sequelae of cervical anastomotic leakage are claimed to be less severe. The ICAN trial showed that intrathoracic anastomosis resulted in better outcome for patients treated with transthoracic minimally invasive esophagectomy for mid to distal EC, but no upper EC were included in this trial (Van Workum 2021).

Minimally Invasive Surgery

Open esophagectomy (OE) is traditionally performed but associated with considerable morbidity due to its highly invasive approach. Minimally invasive alternatives using thoracoscopy and laparoscopy have been increasingly adopted for esophageal surgery to reduce the physiological stress response to trauma and postoperative pain to promote recovery. Minimally invasive esophagectomy (MIE) describes an esophagectomy procedure that avoids the invasiveness of thoracotomy and laparotomy by performing thoracoscopy and laparoscopy instead. MIE is associated with fewer postoperative pulmonary infections, less blood loss, shorter hospitalization, lower pain scores, and better quality of life on short terms (Mariette 2019). As no differences were found in three-year overall and disease-free survival it suggests that MIE provides short-term advantages while maintaining oncological standards (Biere 2012).

As the worldwide implementation of MIE has reached an advanced stage, MIE is a complex procedure with a learning curve that only reaches a plateau after more than 100 cases. The thoracoscopic part of MIE is particularly difficult to master, thus hybrid procedures (either laparoscopy or thoracoscopy) have been introduced. For surgeons in low-volume centers who would face challenges in completing their thoracoscopic/laparoscopic learning phase owing to insufficient caseload, this could be a viable alternative (Mariette 2019).

1 Morbidity and Mortality Outcomes

Outcome reporting after esophageal cancer surgery is heterogeneous. As mentioned earlier, different surgical/anastomotic techniques have differences in postoperative morbidity and mortality. The overall incidence of postoperative complications varies widely between 40–65% and includes systemic complications as well as complications specific to the surgical procedure (e.g. anastomotic leaks, recurrent laryngeal nerve injury). Pulmonary complications are the most common postoperative complications, occurring in 16–40% of patients, but anastomotic leak is the most dreaded, occurring in 5–30% of the patients. In Table 5, the outcomes of cornerstone trials in comparing new surgical techniques versus OE are summarized (Biere 2012; Mariette 2019; Van der Sluis 2019).

A standardized list of complications was only created in 2015, to provide a template for recording individual complications associated with esophagectomy. These quality parameters were documentation on mortality, comorbidities, completeness of data collection, blood transfusion, grading of complication severity, changes in level of care, discharge location, and readmission rates (Low 2015).

Summary

1. For intramucosal ESCC, endoscopic resection (ER) is the standard treatment. Adjuvant therapy is indicated in tumors with unfavorable pathological characteristics (lymphovascular invasion, poor differentiation grade) and for incomplete endoscopic resections.
2. Patients with cT1-2 ESCC without nodal involvement qualify for surgery in Asian practice; in the Western world, neoadjuvant treatment followed by surgery is indicated for T2 or higher and/or N1 cancers.
3. A three-field lymph node dissection is often performed in Asia, but is not outside Asia given the increased risk of postoperative complications. A transthoracic esophagectomy with two-field nodal dissection is standard treatment in the West.
4. An intrathoracic anastomosis results in better outcomes compared to a cervical anastomosis for mid to distal esophageal cancer.
5. A standardized list of complications and its definitions was created in 2015. Before that, outcomes were heterogeneous and lacks methodological rigor.

Section 7 Curative Treatment Part II

Worldwide, there are different paradigms in the curative treatment of ESCC. In general, multimodality treatment offers the best chance for cure. The European Society for Medical Oncology (ESMO) and Nation Comprehensive Cancer Network (NCCN) guidelines recommends neoadjuvant chemoradiotherapy (nCRT) over neoadjuvant chemotherapy (nCT) as curative therapy for esophageal cancer, as this results in better local tumor control through high radical resection rates and better survival (Lordick 2016) (Ajani 2019). In addition to nCRT, definitive chemoradiation (dCRT) is also a potentially curative treatment option according to The American Society of Clinical Oncology (ASCO) (Shah 2020). This is in line with the recommendation of the Nation Comprehensive Cancer Network (NCCN) which also prefers neoadjuvant chemoradiotherapy for curable locally advanced esophageal tumors.

Table 5 An overview of neoadjuvant and adjuvant therapies.

First author	Accural period	Stages enrolled	Chemotherapy	Radio-therapy	Surgery	No. of patients		Survival		P-value
Neoadjuvant chemoradiotherapy vs. surgery alone										
Cao (Cao 2009)	1991–2000	II, III, IV	Mitomycin (10 mg/m^2) Cisplatin (20 mg/m^2) x 5 5-FU (500 mg/m^2) x 5 × 2 cycles	40 Gy	TTE	116	87	3y-OS: 73.3%	3y-OS: 53.4%	< 0.005
Bosset (Bosset 1997)	1989–1995	I, II	Cisplatin (80 mg/m^2) x 2 cycles	37 Gy	TTE	143	139	MST: 18.6 mo	MST: 18.6 mo	0.78
Yang (Yang 2018)	2007–2014	IIB, III	Cisplatin (75 mg/m^2) Vinorelbin (25 mg/m$^{2 \times 2}$) x 2 cycles	40 Gy	TTE	185	227	MST: 100.1 mo	MST: 66.5 mo	0.025
Hagen (Van Hagen 2012)	2004–2008	I, II, III	Carboplatin (AUC 2 mg/ml) Paclitaxel (50 mg/m^2) x 5 cycles	41.4 Gy	TTE and THE	168	186	MST: 49.4 mo	MST: 24 mo	0.003
Lee (Lee 2004)	1999–2002	II, III	Cisplatin (60 mg/m^2) 5-FU (1000 mg/m^2) x 2 cycles	45.6 Gy	TTE	35	48	MST: 28.2 mo	MST: 27.3 mo	0.69 study stopped
Neoadjuvant chemoradiotherapy vs. neoadjuvant chemotherapy										
Wang (Wang 2021)	2017–2018	I, II, III	Cisplatin (25 mg/m^2) Paclitaxel (50 mg/m^2) x 2 cycles	40 Gy	TTE and THE	114	108	1y-OS: 87.1%	1y-OS: 82.6%	0.30
Neoadjuvant doublet chemotherapy vs. triplet chemotherapy										
Kato (Ken 2022)	2012–2018	IB, II, III	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) or Cisplatin (75 mg/m^2) 5-FU (750 mg/m^2) Docetaxel (70 mg/m^2)	-	-	199	202	3y-OS: 72.1%	62.6%	0.006
Neoadjuvant chemotherapy vs. adjuvant chemotherapy										
Ando (Ando 2012)	2000–2006	II, III	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) x 2 cycles	-	TTE	Pre-op 149	Post-op 157	Pre-op 5y-OS: 55%	Post-op 5y-OS: 43%	0.004
Adjuvant chemotherapy vs. surgery alone										
Zhang (Zhang 2014)	1995–2012	II, III, IV	Different regimens	-	THE	887	1160	Not stated	Not stated	0.25

TTE: transthoracic esophagectomy; THE: transthoracic esophagectomy; MST: median survival time; OS: overall survival.

Whereas the preoperative treatment in the West preferably consists of a combination of chemotherapy and radiotherapy, the Asian guideline edited by the Japan Esophageal Society prefers chemotherapy alone followed by radical resection, based on concerns about higher postoperative complication rates (Kitagawa 2019).

Neoadjuvant Therapy

i Neoadjuvant Chemoradiotherapy

The neoadjuvant combination of chemotherapy and radiotherapy aims to achieve improved local and systemic disease control, while exploiting the potent radiosensitizing properties of several chemotherapeutic agents (Wilson 2006). Numerous studies comparing nCRT followed by surgery with surgery alone in patients with ESCC have been reported.

A Chinese study investigated the effect of neoadjuvant chemotherapy (mitomycin, cisplatin and 5-FU), neoadjuvant radiotherapy (40 Gy), nCRT (using the same cytostatics with concurrent 40 Gy irradiation) or surgery alone on survival in patients with locally advanced ESCC (Cao 2009). This study showed a significantly higher three-year survival both in patients treated with radiotherapy (69%) and in those treated with chemoradiotherapy (74%) before surgery, compared to chemotherapy (57%) and surgery alone (53%). However, one-year and five-year survival rates did not differ between these four groups. The suboptimal power of the study complicates correct interpretation and implementation of these data.

Notwithstanding these inconclusive study results, there have been many studies which investigated survival in patients treated with neoadjuvant chemoradiotherapy followed by surgery compared to surgery alone. In 1997, a French study group conducted a multicenter, randomized trial comparing nCRT (cisplatin with concurrent 37 Gy irradiation) plus surgery with surgery alone in patients with stage I-II ESCC (Bosset 1997). This study showed a prolonged disease-free survival (DFS) and longer interval free of local disease (RR = 0.6, 95% CI 0.4–0.9, p = 0.003), but overall survival (OS) was not improved. Postoperative mortality was higher in the nCRT group compared to surgery alone (12% vs. 3.6%), mostly due to respiratory insufficiency and mediastinal infection or sepsis. Another study group performed a randomized trial comparing a different nCRT regimen (vinorelbine and cisplatin with concurrent 40 Gy irradiation) plus surgery with surgery alone (Yang 2018). The primary endpoint OS was significantly improved in patients treated with nCRT and surgery over surgery alone (median 100.1 vs. 66.5 months). Also DFS was longer in patients treated with neoadjuvant chemoradiotherapy (median 100.1 vs. 41.7 months). Contrary to the French trial, postoperative mortality did not differ between both treatment arms. The CROSS study from a research group from the Netherlands randomly assigned patients with resectable esophageal cancer to receive surgery alone or weekly administration of carboplatin (AUC 2mg/ml) and paclitaxel (50 mg/m2) for 5 weeks with concurrent 41.4 Gy radiotherapy (in 23 fractions, 5 days per week), followed by surgery (Van Hagen 2012). The updated results after reaching 10-year follow-up data showed better OS in ESCC patients treated with nCRT plus surgery (46%) compared to surgery alone (23%) (p = 0.061) (Eyck et al. 2021b). Despite the positive effect of chemoradiotherapy on synchronous locoregional plus distant relapse (13% vs. 22%), isolated distant relapse was comparable between both treatment groups (27% vs. 28%). Of 178 patients in the chemoradiotherapy plus surgery arm, 8 patients died related to treatment and of 188 patients in the surgery arm, 7 patients died related to treatment.

Contradictory to these results, a Korean study in patients with stage II-III ESCC showed an excessive locoregional failure rate in patients treated with neoadjuvant chemoradiotherapy (cisplatin, 5-FU with concurrent 45.6 Gy irradiation compared to surgery alone (22% vs. 12%, p = 0.31)) (Lee 2004). Therefore, the authors conclude that neoadjuvant chemoradiotherapy provided no survival benefit for resectable ESCC. Remarkably, the majority of patients in this study did not undergo surgery, resulting in an unexpectedly high drop-out rate for surgery of 31%. This may be an explanation for these unexpected findings which are opposite to other neoadjuvant chemoradiotherapy trials where approximately 80% of patients underwent surgery after chemoradiation.

A multicenter randomized clinical trial performed between 2017 and 2018 in China compared safety and efficacy of nCRT with neoadjuvant chemotherapy followed by minimally invasive esophagectomy (MIE) in patients with potentially curable ESCC (Wang 2021). The chemotherapy, based on paclitaxel (50 mg/m2) and cisplatin (25 mg/m2), was administered to both groups, while 40 Gy of concurrent radiotherapy was added for the neoadjuvant chemoradiotherapy group. One-year overall survival was 87.1% in the neoadjuvant chemoradiotherapy group and 82.6% in the neoadjuvant chemotherapy group (p =0.30). Postoperative morbidity, mortality and complications did not significantly differ between both groups.

In summary, several studies with all different chemotherapy and radiotherapy regimens have shown the positive effect of nCRT plus surgery on survival in ESCC patients as compared to surgery alone. The various nCRT regimens have not been compared head-to-head, and the fact that the Dutch CROSS regimen is favored in large parts of the Western world is mostly explained by its low toxicity rates and the absence of a negative effect on postoperative mortality.

ii Chemotherapy with Concurrent Proton-based Radiation

Over the past decades, multiple studies focused on proton-based radiation in combination with chemotherapy for esophageal cancer. Proton-based radiotherapy provides dosimetric sparing of vital structures and organs surrounding the tumor which could potentially result in less radiation-related toxicities and postoperative complications. A recent randomized phase-II trial compared total toxicity burden and PFS between proton beam therapy (PBT) and intensity-modulated radiation (IMRT) in patients with esophageal cancer (Lin 2020). Patients were randomly assigned to PBT or IMRT (50.4 Gy). Total toxicity burden (TTB) consisted of the cumulative adverse events severity experienced by patients. Patients receiving IMRT experienced an average TTB score that was 2.3 times higher than PBT (39.9 vs. 17.4). The mean postoperative complication score was 7.6 times higher for patients treated with IMRT compared to PBT (19.1 vs. 2.5). No statistically differences were seen in PFS, OS or quality of life (based on EQ-5D). This study support treatment toxicity benefit of PBT compared to IMRT. However, further validation of these results is required within a phase-III trial to see whether OS after treatment with PBT is non-inferior to IMRT.

iii Neoadjuvant Chemotherapy

In Japan, (neo)adjuvant chemotherapy (nCT) is considered to be standard of care for esophageal cancer patients, in part explained by concerns about postoperative mortality following nCRT. Followed by a three-field lymphadenectomy, patients treated with nCT have non-inferior oncological outcomes compared to treatment strategies including irradiation. The JCOG1109 trial compared doublet and triplet chemotherapy and chemoradiotherapy in patients with ESCC stage IB-III, including overall survival as primary endpoint (Ken 2022). Patients were randomly assigned to neoadjuvant doublet chemotherapy (cisplatin 80 mg/m^2 on day 1, 5-FU 800 mg/m^2 on day 1–5 Q3W/2 course), triplet chemotherapy (docetaxel 70 mg/m^2 on day 1, cisplatin 70 mg/m^2 on day 1 and 5-FU 750 mg/m^2 on day 1–5 Q3W/3 course) or chemoradiotherapy (cisplatin 75 mg/m^2 on day 1, 5-FU 1000 mg/m^2 on day 1–4 Q4W/2 course with concurrent 41.4 Gy radiation). The three-year overall survival was significantly increased in patients treated with triplet chemotherapy compared to doublet chemotherapy (72.1% vs. 62.6%, HR 0.68; 95% CI 0.50–0.92, p = 0.006) with no significant difference in toxicity. As a result of this trial, triplet chemotherapy could be considered as potential neoadjuvant regimen for patients with locally advanced ESCC.

While neoadjuvant chemoradiation treatment predominates in Western countries, the place for nCT remains uncertain. Efforts have been made to establish whether neoadjuvant chemotherapy should be preferred over adjuvant chemotherapy. Theoretically, because of the adverse effect of esophagectomy on patient's condition, more patients may be able to complete a neoadjuvant treatment compared to an adjuvant one. Moreover, administering chemotherapy while the primary tumor is still in situ enables response evaluation and assessment of pathological tumor regression, which can be helpful in treatment decisions moving forward. The Japanese study group of Ando et al. initiated a randomized controlled trial to evaluate the optimal timing for perioperative chemotherapy, that is, before or after surgery (Ando 2012). Patients with ESCC clinical stage II/III, excluding cT4, were randomized to undergo surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by surgical resection. Chemotherapy consisted of two courses of cisplatin (80 mg/m^2) on day one and 5-FU (800 mg/m^2 per continuous infusion) over days 1–5 × 2 courses with a three-week interval. Primary endpoint was progression-free survival (PFS), measured from the date of randomization to the date of first evidence of relapse or death due to any cause. The primary endpoint did not reach statistical significance, but the five-year OS in patients treated with nCT was superior to that with adjuvant chemotherapy (55% vs. 42%, HR 0.73, 95% CI 0.54–0.99, p = 0.04). No difference was described in postoperative morbidity between the two groups. There are several possible reasons to explain the better OS in patients treated with neoadjuvant chemotherapy. First, neoadjuvant chemotherapy can lead to tumor down-staging as shown by the equivalent amount of patients with clinical stage II ESCC at baseline compared to higher proportion of pathological stage II ESCC or lower in this group. In addition, R0 resection was slightly more frequent in the group of patients treated with neoadjuvant chemotherapy. Third, completion of the full chemotherapy regimen was much better in the neoadjuvant chemotherapy group (85.4% vs. 75%, p = 0.04). Hence, optimal timing of treatment with chemotherapy seems to be before surgical resection. However, a letter to the authors rightly noted that in the adjuvant treatment arm, only node-positive patients were treated with chemotherapy, while in the neoadjuvant treatment arm both node-positive and node-negative patients were treated (Ajani and Swisher 2012). Because of this imbalance in treatment arms, drawing a conclusion about the timing of chemotherapy remains challenging.

Adjuvant Therapy

Very few meta-analyses or reviews have been published on the value of adjuvant CT for ESCC, a strategy which is more commonly used in the East than in the West. Not only are Western-oriented guidelines more reluctant to make a recommendation about adjuvant chemotherapy in esophageal cancer (ESMO, NCCN, ASCO), the evidence in Asian guidelines are only showing recommendations based on weak evidence (Ajani 2019; Kitagawa 2019; Lordick 2016; Shah 2020).

An Asian study group performed a meta-analysis of randomized controlled trials and non-randomized studies in 2014, including 2047 patients (Zhang 2014). All studies compared surgery plus adjuvant chemotherapy with surgery alone in patients with resectable ESCC. The regimen of cisplatin plus 5-FU was predominantly used with cisplatin dose ranging from 70 mg/m2 to 120 mg/m2, in varying but mostly three-weekly schedules. The studies were also heterogeneous in their predominant surgical technique, as both two-field and three-field lymphadenectomies were performed. There was no statistically significant benefit in three-year OS for adjuvant chemotherapy (RR = 0.89, 95% CI 0.72–1.09; p = 0.25); an effect was seen on 1-year DFS (RR = 0.68, 95% CI 0.51–0.89; p= 0.006) but not on three-year DFS (RR = 0.97, 95% CI 0.73–1.29; p = 0.84). This may be explained by the fact that the effect of chemotherapy can extinguish over time.

The benefit of adjuvant immunotherapy has been proven in the randomized controlled CheckMate 577 trial (Kelly 2021). Patients with resected (R0) stage II or III esophageal or gastroesophageal junction cancer who had received nCRT and had residual pathological disease were given nivolumab (at a dose of 240 mg every 2 weeks for 16 weeks, followed by nivolumab at a dose of 480 mg every 4 weeks) or placebo. The median disease-free survival was significantly longer in patients who received nivolumab (22.4 months versus 11.0 months; p<0.001). This treatment strategy is already available in many regions even before the long-term results has been published.

Definitive Chemoradiotherapy

Definitive chemoradiation (dCRT) has been the mainstay for the non-operative management of localized esophageal cancer after several RCTs revealed its superiority to radiation alone, and it represents a standard of care in both Europe and the US. Patients may be considered unfit for surgical resection due to overall frailty or cardiopulmonary comorbidities, since surgery is associated with substantial perioperative complications. Furthermore, dCRT constitutes the treatment of choice for tumors (usually SCC) of the cervical esophagus, where radical surgery requires concomitant removal of the larynx and is associated with a chronically elevated risk of aspiration and severe impact on quality of life (Allum 2011). dCRT is also used in the management of advanced locoregional disease, including potentially resectable (T4a) and unresectable (T4b) primary disease (Jeene 2018).

According to the ESMO guideline, dCRT consisting of cisplatin/5-FU combined with radiation doses of 50.4 Gy in fractions of 1.8 Gy is regarded as standard, while alternatively six cycles of FOLFOX can be given (Lordick 2016). The NCCN panel prefers the combination of paclitaxel and carboplatin for dCRT, as well as the combination of FOLFOX and 5-FU plus cisplatin, although FOLFOX alone is associated with less treatment-related adverse events (Ajani 2019). The ASCO and the Asian guidelines both do not favor any treatment regimen for dCRT (Kitagawa 2019; Shah 2020).

dCRT has not been directly compared to nCRT or chemotherapy plus surgery in patients with resectable tumors. Therefore, in patients with a potentially resectable tumor but concerns about the feasibility of major surgery given a frail condition or significant comorbidities, the optimal choice of therapy should be weighed on an individual patient basis (Table 6).

The RTOG 85–01 trial randomly assigned 123 patients (88% with squamous histology) with T1-3N0-1M0 tumors to receive either dCRT or radiotherapy alone (Cooper 1999). CRT consisted of cisplatin at a dose of 75 mg/m2 on day one and infusional 5-FU at a dose of 1000 mg/m2/24h on days 1–4 repeated in weeks 1, 5, 8, 11 (four courses) with radiation therapy commencing on day one and consisting of a total dose of 50 Gy in 25 fractions (5 fractions per week, 2 Gy per fraction). The radiotherapy control arm consisted of a high total dose of 64 Gy, delivered in doses of 2 Gy per fraction. Randomization was suspended after inclusion of 90 patients, given the results of the interim analysis which showed statistically different survival rates in favor of the combined modality therapy arm. A statistically significant five-year OS benefit was seen in favor of CRT

Table 6 An overview of definitive chemoradiotherapy.

			Regimen 1		Regimen 2						
First author	**Accural period**	**Stages enrolled**	**Chemotherapy**	**Radio-therapy**	**Chemotherapy**	**Radio-therapie**	**No. of patients**		**Survival**		**P-value**
Definitive chemoradiotherapy vs. radiotherapy alone											
Cooper (Cooper 1999)	1985–1990	I, II, III	Cisplatin (75 mg/m^2) 5-FU (1000 mg/m^2) x 4 cycles	50 Gy	-	64 Gy	36	58	5y-OS: 26%	5y-OS: 0%	Not stated
Definitive chemoradiotherapy											
Minsky (Minsky 2002)	1995–1999	I, II, III	Cisplatin (75 mg/m^2) 5-FU (1000 mg/m^2)	64.8 Gy	Cisplatin (75 mg/m^2) 5-FU (1000 mg/m^2)	50.4 Gy	109	109	MST: 13 mo	MST: 18.1 mo	Not stated
Hulshof (Hulshof 2021)	2012–2018	I, II, III, IV	Carboplatin (AUC 2 mg/ml) Paclitaxel (50 mg/m^2) x 6 cycles	50.4 Gy	Carboplatin (AUC 2 mg/ml) Paclitaxel (50 mg/m^2) x 6 cycles	61.6 Gy	130	130	3y-PFS: 75%	3y-PFS: 79%	0.11

MST: median survival time; OS: overall survival; PFS: progression-free survival; CT: chemotherapy.

(26% vs. 0%). The authors concluded that a combination of CRT increases the survival compared with radiotherapy alone.

However, the dose of radiation and the choice of chemotherapeutic agents remain a matter of debate, and the guidelines are not unequivocal about this. Several randomized trials have attempted to determine the optimal CRT regime for patients undergoing dCRT. The INT 0123 trial included 236 patients with cT1-4N0-1M0 esophageal cancer who were treated with combined-modality therapy, consisting of four-monthly cycles of 5-FU (1000 mg/m2/24h) and cisplatin (75 mg/m2 bolus day 1) with concurrent 64.8 Gy radiotherapy versus the same chemotherapy regimen with a lower dose of concurrent 50.4 Gy radiotherapy (Minsky 2002). This study showed no significant difference in median survival (13.0 vs. 18.1 months), two-year survival (31% vs. 40%) or locoregional recurrence (56% vs. 52%) between normal-dose or high-dose therapies. Therefore, the authors concluded that 50.4 Gy radiotherapy should be considered as standard radiation dose for patients treated with dCRT.

The ARTDECO study investigated the effect of radiation dose escalation on local tumor control in dCRT for patients with inoperable and/or unresectable esophageal carcinoma (Hulshof 2021). Patients were randomly assigned between standard dose of radiotherapy (50.4 Gy in 1.8 Gy fractions) or high dose radiotherapy (61.6 Gy in 2.2 Gy fractions) to the primary tumor. The chemotherapy regimen consisted of carboplatin (AUC 2) and paclitaxel (50 mg/m2) in both treatment arms. The primary endpoint, three-year local PFS, did not statistically differ between both treatment arms in ESCC (75% in the standard dose arm vs. 79% in the high dose treatment arm). The absence of a dose effect indicates that the current radiation dose of 50.4 Gy does not require modification.

Summary

1. Whereas preoperative treatment in the West preferably consists of chemoradiotherapy, Eastern countries still prefer chemotherapy.
2. Adjuvant therapy is more commonly used in the East than in the West, but little is known about the true benefit.
3. Definitive chemoradiotherapy is the mainstay for non-operative management of ESCC, but guidelines are not unequivocal on the dose of radiation and choice of chemotherapeutic agents.

Section 8 Palliative Treatment

Palliative Treatment

A Chemotherapy

While the benefit of systemic chemotherapy is limited compared to treatment of other malignancies of the digestive tract, chemotherapy can be a valid option for patients with a good performance status and metastatic ESCC. The aim is to prolong survival, improve and maintain quality of life, and ameliorate disease-related symptoms. Most commonly, a platinum compound (oxaliplatin, carboplatin, or cisplatin) is combined with 5-fluorouracil (5-FU), capecitabine or a taxane (Janmaat 2017). This section focuses on established regimens as well as current trends in the use of chemotherapy for patients with unresectable or metastatic ESCC (Table 7).

i First-line Therapy

Combination of Chemotherapeutic Agents

The most widely studied chemotherapeutic agent is cisplatin, which has been in use since the early 1980s and forms the basis of many of the combination regimens used in this disease. The effectivity of cisplatin and 5-fluorouracil (5-FU) has mostly been investigated as neoadjuvant treatment, but data are also available on their role in the palliative setting. Studies showed that the treatment combination of 5-FU with cisplatin improve response rates compared to cisplatin alone, but no survival benefit was seen. A randomized phase-II study in patients with locally advanced or metastatic ESCC treated with combined cisplatin (100mg/m^2 on day 1) and 5-FU (1000mg/m^2 day 1–5) or cisplatin alone was performed in 1997 (Bleiberg 1997). Response to therapy was determined using radiological and endoscopic diagnostic modalities, the latter of which is not a standard method to determine response to systemic therapy in advanced disease. Of 88 included patients, 35% responded to the combination therapy whereas 19% responded to cisplatin alone. The one-year and two-year survival in the combination therapy arm was numerically higher (34% and 18%) compared to patients treated with cisplatin alone (27% and 9%), respectively. Toxicity was more frequent and more treatment-related deaths were observed after combined therapy. Based on the toxicity of the regime, the authors conclude that combined therapy with cisplatin and 5-FU is not recommended. This is in line with the results of a randomized phase-II French study, comparing 5-FU (1000mg/m^2 day 1–5) and cisplatin (single dose of 100mg/m^2 or 20 mg/m^2/day spread over 3 hours for 5 days) with no chemotherapy as palliative therapy for ESCC (Levard 1998). This study included patients in the curative setting, who received the chemotherapy after oncologic primary tumor resection, as well as patients with unresectable or metastatic tumors. In the 36 patients who did not undergo surgical resection because of advanced or metastatic disease, median overall survival was not significantly longer in patients treated with chemotherapy compared to the control group (both 12 months). However, significantly more patients experienced hematological and renal adverse

Table 7 An overview of palliative therapeutic regimens.

First author	Accural period	Therapy	Regimen 1	Regimen 2	No. of patients		Survival		P-value
Dual chemotherapy vs. single chemotherapy									
Bleiberg (Bleiberg 1997)	1985–1989	First-line	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2)	Cisplatin (100 mg/m^2)	44	44	2y-OS: 27%	2y-OS: 9%	Not stated
Chemotherapy alone									
Levard (Levard 1998)	1987–1992	First-line	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2)	No chemotherapy	72	84	MST: 20 mo	MST: 20 mo	Not stated
Polee (Polee 2004)	Not stated	First-line	Cisplatin (60 mg/m^2) Paclitaxel (180 mg/m^2)	-	51	-	MST: 9 mo 1y-OS: 43%	-	N/A
PD-1 inhibitors									
Sun (Sun 2021)	2017–2019	First-line	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) Pembrolizumab (200 mg)	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) Placebo	373	376	MST: 13.9 mo	MST: 8.8 mo	< 0.0001
Rui-hua (Rui-Hua 2021)	2018–2020	First-line	Cisplatin (75 mg/m^2) Paclitaxel (175 mg/m^2) Camrelizumab 200 mg	Cisplatin (75 mg/m^2) Paclitaxel (175 mg/m^2) Placebo	298	297	MST: 15.3 mo	MST: 12.0 mo	0.0010
Shen (Shen 2021)	Not stated	First-line	Cisplatin (75 mg/m^2) Paclitaxel (175 mg/m^2) Sintilimab (200 mg)	Cisplatin (75 mg/m^2) Paclitaxel (175 mg/m^2) Placebo	327	332	MST: 16.7 mo	MST: 12.5 mo	< 0.0001
Immunotherapeutic agents									
Doki (Doki 2022)	2017–2019	First-line	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) Nivolumab (240 mg)	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2)	321	324	MST: 15.4 mo	MST: 9.1 mo	< 0.0001
		First-line	Nivolumab (240 mg) Ipilimumab (1 mg/kg)	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2)	325	324	MST: 13.7 mo	MST: 9.1 mo	0.0010
EGFR inhibitors									
Lorenzen (Lorenzen 2009)	2004–2006	First-line	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2) Cetuximab (400 mg/m^2)	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2)	32	30	MST: 9.5 mo	MST: 5.5 mo	0.32
Moehler (Moehler 2020)	2012–2015	First-line	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2) Panitumumab (9 mg/kg)	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2)	73	73	MST: 9.4 mo	MST: 10.2 mo	0.43
Second-line regimens									
Dutton (Dutton 2014)	2009–2011	Second-line	Gefitinib (500 mg)	Placebo	224	225	MST: 3.73 mo	MST: 3.67 mo	0.29
Kato (Kato 2019)	2016–2017	Second-line	Nivolumab (240 mg)	Paclitaxel (100 mg/m^2) or Docetaxel (75 mg/m^2)	210	209	MST: 10.9 mo	MST: 8.4 mo	0.019
Kojima (Kojima 2020)	2015–2017	Second-line	Pembrolizumab (200 mg)	Paclitaxel (80–100 mg/m^2) or Docetaxel (75 mg/m^2) or Irinotecan (180 mg/m^2)	314	314	MST: 8.2 mo	MST: 7.1 mo	0.0095

(Continued)

Table 7 (Continued)

First author	Accural period	Therapy	Regimen 1	Regimen 2	No. of patients		Survival		P-value
Third-line regimens									
Kato (Ken 2021)	2014	Third-line	Nivolumab (3 mg/kg)	-	65	-	MST: 10.8 mo 5y-OS: 6.3%	-	N/A
Shah (Shah 2019)	2016–2017	Third-line	Pembrolizumab (200 mg)	-	121	-	ORR: 14.3%	-	N/A

MST: median survival time; OS: overall survival; ORR: objective response rat

events as well as polyneuropathy with chemotherapy. Thus, in this small study, combined 5-FU and cisplatin did not have benefit over best supportive care. Of note, both in the 1997 and the French study the cisplatin dose was higher than what is nowadays commonly used in palliative chemotherapy combinations. Furthermore, DPYD (deleterious polymorphisms in the gene encoding dihydropyrimidine dehydrogenase) genotyping to identify patients at increased risk of 5-FU toxicity was not implemented in clinical practice. Both these factors will have affected the rate of adverse events in these studies.

A phase-II study performed in the Netherlands in 2002 investigated the efficacy of a bi-weekly combination of paclitaxel (180 mg/m^2) and cisplatin (60 mg/m^2) in patients with metastatic or unresectable adenocarcinoma, undifferentiated- or SCC of the esophagus or junction (Polee 2002). Patients were evaluated after three and six cycles and responding patients received a maximum of eight cycles. All included patients received at least three cycles of chemotherapy. The median survival was 9 months (range 2–29 months), with a one-year survival rate of 43%. Sensory neurotoxicity was the predominant toxicity; grade 2 neurotoxicity was seen in 20% of patients. This study shows that the combination of paclitaxel and cisplatin is relatively well tolerated and has promising efficacy (Polee 2004). A slightly adapted regime of weekly carboplatin (AUC 4) and paclitaxel (100 mg/m^2) was investigated in a phase-I trial, with better tolerance and equally promising activity. These treatment regimens were never investigated in a phase-III randomized trial.

Overall, data on palliative chemotherapy for ESCC are scarce, do not show unequivocal proof for survival benefit and come from smaller and older trials. Therefore, best supportive care alone or treatment in a clinical trial should also be considered as valid treatment options in the absence of other treatment options such as immunotherapy.

Chemotherapy Plus PD-1 Inhibitors

As discussed earlier, chemotherapy alone is of limited effect, and based on its paradigm-changing efficacy in other solid tumors, the value of immune checkpoint inhibitors when added to palliative chemotherapy has been investigated in several large clinical trials. Immune checkpoint inhibitors, in the form of PD-(L)1 or CTLA4-inhibitors, is effective through activation of an antitumor response by the patient's own immune system.

One of the pivotal trials is the KEYNOTE-590 trial, which is a randomized phase-III study investigating first-line chemotherapy with or without pembrolizumab for advanced unresectable or metastatic esophageal cancer (Sun 2021). This study included 749 patients, of whom almost 75% had ESCC. All patients were treated with pembrolizumab (200 mg) or placebo, plus 5-fluorouracil (800 mg/m^2 day 1–5) and cisplatin (80 mg/m^2 day 1 every 3 weeks), once every 3 weeks for up to 35 cycles. The dual primary endpoints of this study were OS and PFS, which were tested according to seven primary hypotheses in all included patients; those with PD-L1 combined positive score (CPS) ≥ 10 and ESCC patients OS was superior for pembrolizumab plus chemotherapy in patients with PD-L1 CPS ≥ 10 with a median OS of respectively 13.9 vs. 8.8 months (HR 0.57, 95% CI 0.43–0.75). In the other patient subgroups such as those with adenocarcinomas or ESCC and PD-L1 CPS < 10, median PFS was increased but no OS benefit was seen. Addition of pembrolizumab seems to be particularly effective in the (in this trial) 30% of patients with ESCC who had a CPS score ≥ 10.

The phase-III ESCORT-1st study investigated the efficacy and safety of camrelizumab plus chemotherapy vs. chemotherapy alone in patients with untreated advanced or metastatic ESCC (Rui-Hua 2021). Patients were randomized to receive camrelizumab 200 mg or placebo, both combined with 6 cycles of paclitaxel (175 mg/m2) and cisplatin (75 mg/m2). Primary endpoints were OS and PFS. With a median follow-up of 10.8 months, camrelizumab plus chemotherapy significantly improved

OS compared with placebo plus chemotherapy (median 15.3 months vs. 12 months, HR 0.70, 95% CI 0.56–0.88). Camrelizumab plus chemotherapy showed also superior PFS compared to placebo plus chemotherapy (median 6.9 months vs. 5.6 months, HR 0.56, 95% CI 0.46–0.68). Treatment-related adverse events were comparable between both treatment arms. As result of this study, FDA approval was requested from the China National Medical Products Administration for camrelizumab plus chemotherapy in untreated advanced or metastatic ESCC.

More recent, the first results of the ORIENT-15 were published (Shen 2021). This study randomized patients with unresectable locally advanced, recurrent of metastatic ESCC either to sintilimab (200 mg) or placebo, both combined with chemotherapy (paclitaxel 175 mg/m2 and cisplatin 75 mg/m^2). The primary endpoint was OS in patients with PD-L1 CPS ≥ 10 and all patients. Secondary endpoints include PFS and ORR. Sintilimab plus chemotherapy was superior for OS compared to placebo plus chemotherapy in all patients (median 16.7 months vs. 12.5 months, HR 0.628, 95% CI 0.508–0.777) and patients with CPS ≥ 10 (median 17.2 months vs. 13.6 months, HR 0.638, 95% CI 0.480–0.848). ORR was 75.5% vs. 56.9% in all patients and PFS was also superior in patients treated with sintilimab plus chemotherapy (median 7.2 months vs. 5.7 months, HR 0.558, 95% CI 0.461–0.676, $p < 0.0001$). Treatment-related adverse events were similar between both groups. The results of this trial are promising for first-line treatment with sintilimab plus chemotherapy.

Combination of Immunotherapeutic Agents

Recently, the results of the Checkmate 648 study were reported. This randomized, open-label phase-III study was performed in patients with unresectable advanced, recurrent or metastatic ESCC (Doki 2022). Primary endpoints were OS and PFS in subjects with PD-L1 expressing tumors (≥ 1%). Patients were randomly assigned to either cisplatin (80 mg/m^2) and 5-FU (800 mg/m^2) in a 4-weekly schedule or to cisplatin, 5-FU plus nivolumab (240 mg 2qw) or nivolumab (same dose) plus ipilimumab (a CTLA-4 inhibitor, at 1 mg/kg q6w). Superior OS was seen in patients with tumor cell PD-L1 ≥ 1% treated with chemotherapy plus nivolumab (median 15.4 months) compared to CT alone (median 9.1 months) (HR 0.54, 99.5% CI 0.37–0.80). Patients with tumor cell PD- L1 ≥ 1% treated with nivolumab and ipilimumab had significant improved OS as well compared to CT alone (median 13.7 months vs. 9.1 months respectively, HR 0.64, 98.6% CI 0.46–0.90). The efficacy of the combined immunotherapy regimen versus the CT plus immunotherapy regimen was not compared directly. The incidence of grade ¾ treatment-related adverse events was highest in patients treated with CT plus nivolumab, and numerically lowest in patients treated with dual immunotherapy, while treatment-related serious adverse events were numerically more common in the dual immunotherapy arm. Depending on patient characteristics and assuming positive decisions by the regulatory agencies, both combinations represent a new potential standard of care.

Chemotherapy Plus Target Epidermal Growth Factor Receptor (EGFR)

Recently, studies focused on therapeutic agents that enhances the antitumor effect of chemotherapy are gaining interest. Agents targeting the EGFR have been successfully implemented in clinical practice for colorectal and lung cancer. The efficacy of EGFR inhibitors is precluded to those patients whose tumor is KRAS wild type, as tumors with a gain-of-function KRAS mutations have a constitutively active pathway downstream of EGFR. In 2009, the additional effect of cetuximab on tumor response was assessed in a randomized phase-II trial in patients with advanced KRAS wild type ESCC who were treated with either triple therapy (cisplatin, 5-FU and cetuximab) or dual therapy (cisplatin and 5-FU) (Lorenzen 2009). Patients received cisplatin (100 mg/m^2 day 1), 5-FU (1000 mg/m^2 at days 1–5) and in case of triple therapy also cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly thereafter. Primary endpoint was tumor response. Overall response rates were 34% in patients treated with additional cetuximab and 30% in cisplatin and 5-FU alone, which is in line with the results of the study of Bleiberg et al. (Bleiberg 1997). This did not translate into a statistically significant increase in median PFS and OS (respectively 5.9 vs. 3.6 months, $p = 0.21$ and 9.5 vs. 5.5 months, $p = 0.32$). In conclusion, cetuximab may increase the response rate of treatment with cisplatin and 5-FU chemotherapy, but based on this phase-II study, no definitive conclusions could be drawn on the effect on survival.

Another German study group investigated the effect of panitumumab on survival in patients with ESCC that was neither curatively resectable nor qualified for definitive chemoradiotherapy (Moehler 2020). Remarkably, KRAS mutation status was assessed nor used as an inclusion criterion. Patients were randomly assigned to cisplatin (100 mg/m^2 day 1) and 5-FU (1000 mg/m^2 per day at days 1–4 of every 3-week cycle) or treatment with combined cisplatin, 5-FU and panitumumab (9 mg/kg on day 1 of 3-week cycle prior to chemotherapy). The trial was terminated prematurely because of high early mortality rate (within 30 days after randomization) as well as an increased frequency of therapy-related serious adverse events in the panitumumab therapy arm and the interim analysis that showed significantly higher median overall survival in favor of the standard therapy arm over panitumumab (HR 1.77, 95% CI 1.06–2.98, p = 0.028). In the final analysis, median OS was 10.2 versus 9.4 months for cisplatin/5-FU versus cisplatin/50FU plus panitumumab, respectively (HR 1.17, 95% CI 0.79–1.75; p = 0.43). Serious adverse events grade 5 were seen in 23.6% of patients treated with panitumumab compared to 4.3% in patients treated with combined chemotherapy only. In conclusion, while the addition of cetuximab may increase response rates, the developments in the anti-EGFR field for esophageal cancer have largely stopped, owing to its lack of impact on survival and substantial toxicity.

ii Second-line Therapy

In 2014, a phase-III randomized placebo-controlled trial was performed among patients with progressive junctional type I/II Siewert tumors after chemotherapy (Dutton 2014). Both esophageal adenocarcinomas and squamous cell carcinomas were included, and no tumor biomarkers were used to select patient subgroups. Patients were randomly assigned to gefitinib (500 mg), an EGFR-inhibitor, or matching placebo and treatment continued till disease progression or unacceptable toxicity occurred. The primary outcome overall survival did not differ between both groups with a median OS of 3.7 months in both groups (HR 0.90, 95% CI 0.74–1.09, p = 0.29). In a post-hoc analysis, patients with EGFR copy number gain as determined by FISH or EGFR amplification did benefit from gefitinib (HR for death 0.59; 95% CI 0.35–1.00, p = 0.05) (Petty 2017). Unfortunately, no prospective trial has been published confirming the benefit of gefitinib in this patient subgroup, and gefitinib has thus not made its way into clinical practice for esophageal cancer.

In 2019, the efficacy of nivolumab was investigated in the ATTRACTION-3 trial (Kato 2019). This multicenter, international phase-III trial included patients' refractory to previous chemotherapy from both eastern and western countries. Patients were randomly assigned to either nivolumab (240 mg for 30 minutes every 2 weeks) or investigator's choice of chemotherapy (paclitaxel 100 mg/m^2 once per week for 6 weeks then 1 week off; or docetaxel 75mg/m^2 every 3 weeks). In total 48% of patients had PD-L1 expression of whom 30% had a CPS score ≥ 10. A slight improvement in median overall survival of 2.5 months was observed in patients who received nivolumab, in comparison with patients who received chemotherapy (HR 0.77 [95% CI 0.62–0.96]; p= 0.019). Progression-free survival was not significantly different between the two treatment arms, and also PD-L1 expression did not identify patients with greater benefit. Fewer grade 3 or 4 treatment-related adverse events were reported in the nivolumab group (18% vs. 63%) which implicates that treatment with nivolumab is safe and may be better tolerated than chemotherapy.

Another study in patients with advanced/metastatic esophageal cancer who had progressed on or after first-line therapy is the KEYNOTE-181 trial (Kojima 2020). This Asian study group conducted an open-label, phase-III study in which patients were randomly assigned to pembrolizumab 200 mg every 3 weeks for up to 2 years or chemotherapy of investigator's choice (paclitaxel, docetaxel or irinotecan). Primary endpoints were OS in patients with PD-L1 combined positive score (CPS) ≥ 10, in patients with squamous cell carcinoma, and in all patients. In patients with PD-L1 CPS ≥ 10, OS was significantly prolonged with pembrolizumab versus chemotherapy (median 9.3 vs 6.7 months; HR 0.69, 95% CI 0.52–0.93; p = 0.0074). In patients with ESCC (64%), the primary endpoint median OS was slightly in favor of treatment with pembrolizumab (8.2 vs. 7.1 months, HR 0.78, 95% CI 0.63–0.96, p = 0.0095). However, in all patients, the median OS was not statistically different between the pembrolizumab group and chemotherapy group, both 7.1 months (HR 0.89, 95% CI 0.75–1.05; p = 0.0560). In conclusion, pembrolizumab showed survival benefit versus chemotherapy as second-line therapy for advanced esophageal cancer in patients with PD-L1 CPS ≥ 10.

iii Third-line Therapy

The ATTRACTION-1 multicenter phase-II trial conducted in Japan evaluated the activity and safety of nivolumab in patients with advanced ESCC refractory or intolerant to fluoropyrimidine-, platinum- and taxane-based chemotherapy (Ken 2021). Patients were treated with 3 mg/kg nivolumab every 2 weeks in 6-week cycles until disease progression or toxicity. The primary endpoint was ORR and the secondary endpoint included OS. After a minimum follow-up of 5 years, 11 out of 64 patients had an objective response (17.2%, 95% CI 9.9–28.2). The median OS was 10.8 months (95% CI 7.4–13.9) and the estimated 5-year OS was 6.3% (95% CI 2.0–14.0). PFS at 5-years was 6.8% (95% CI 2.2–15.1). Diarrhea and rash occur with a frequency of > 10%. This study shows nivolumab as potential third-line treatment option.

Another phase-II study, the KEYNOTE-180, enrolled patients with advanced, metastatic esophageal cancer that progressed after two or more lines of therapy (Shah 2019). Patients were treated with pembrolizumab 200 mg every 3 weeks until disease progression or unacceptable toxic effects, for up to 2 years. Primary endpoint was ORR. Median duration of follow-up was 5.8 months. The ORR was 9.9% (95% CI 5.2–16.7) in all patients and 14.3% (95% CI 6.7–25.4) among patients with ESCC. Only 12.4% of patients had treatment-related adverse events grade 3–5. This study shows the durable antitumor effect of pembrolizumab with manageable safety in pretreated patients with esophageal cancer.

Radiotherapy

Radiotherapy alone has a modest role in the radical management of locally advanced ESCC and is usually reserved for patients who are not considered good candidates for surgery or chemotherapy. If curative treatment is no longer an option due to the extent of the disease, palliative radiotherapy can be useful to relief symptoms (dysphagia and pain) and to improve patients' quality of life.

External-beam Therapy

The use of external-beam radiotherapy is established in the setting of inoperable disease where, at doses of 20 Gy in 5 fractions or 30 Gy in 10 fractions, it can effectively palliate dysphagia and pain. Fractionated external-beam radiotherapy often causes swelling first with increase of dysphagia as a result, followed by sustained relief of dysphagia when swelling decreases.

Although fractioned external-beam radiotherapy is widely used, data on its efficacy is scarce. In 2012, a retrospective review was performed in patients with esophageal cancer unsuitable for radical treatment who underwent external beam radiotherapy (Murray 2012). In total 93% of patients complained of dysphagia prior to radiotherapy. Almost all patients were treated with 20 Gy external-beam radiotherapy in 5 fractions. Improvement in dysphagia was seen in 75% of patients and 31% of patients received additional therapy for palliation. External-beam radiotherapy was well tolerated with 2 patients (1%) failing to complete the full regimen and hospitalization in only 5 patients (3%) with no treatment-related death. The POLDER study group investigated the effect of short-course external beam radiotherapy compared to intraluminal brachytherapy for palliation of dysphagia (Jeene 2020). Improvement of dysphagia was observed in 83% after external beam therapy versus 64% after brachytherapy ($p = 0.048$) and severe toxicity occurred in 3% and 13%, respectively. The authors therefore conclude that external beam therapy is at least as effective as brachytherapy in the palliation of dysphagia.

Another study from Australia randomly assigned patients with advanced or metastatic esophageal cancer to either palliative chemoradiotherapy or radiotherapy alone for treatment of malignant dysphagia (Penniment 2018). Primary endpoint was dysphagia relief at nine weeks and maintenance four weeks later. Complete dysphagia relief was obtained in 26 (24%) of patients treated with radiotherapy alone compared to 32 (29%) of patients treated with chemoradiotherapy ($p = 0.44$). Grade 3–4 toxicity occurred less frequent in patients treated with radiotherapy (16%) compared to chemoradiotherapy (36%) ($p = 0.0017$). Therefore, the authors conclude that radiotherapy alone should be considered a safe and well tolerated treatment option for patients with malignant dysphagia.

In conclusion, external-beam should be considered as safe and well tolerated palliative treatment option for patients with malignant dysphagia. In the same context, endoluminal brachytherapy constitutes an acceptable alternative.

Brachytherapy

Brachytherapy involves endoscopic placement of a radioactive applicator into the esophagus. During endoscopy, the upper and lower tumor borders are marked and dilatation of the malignant stricture could be performed with caution to perforation. This allows treatment with a high radiation dose to a localized area of the esophagus, sparing surrounding structures as much as possible. The European Society for Medical Oncology (ESMO) guideline recommends single-dose brachytherapy after external radiotherapy since it provides better long-term relief of dysphagia (Lordick 2016). The Asian guideline edited by the Japan Esophageal Society concludes that brachytherapy is scarcely performed in Japan and therefore results of several studies have no direct implication for clinical practice (Kitagawa 2019).

In 2017, an Italian study group performed a systematic review to determine the efficacy and safety of brachytherapy in patients with malignant dysphagia (Fuccio 2017). Results of 623 patients were analyzed regarding dysphagia-free survival and adverse event rates. The authors conclude that brachytherapy was highly effective, resulting in six months dysphagia-free survival of 47.4% (95% CI 38.5–56.5). Despite the severe adverse event rate of 22.6% with the main reported adverse events brachytherapy-related stenosis (12.2%) and fistula development (8.3%), it appears to be a relatively safe treatment option which is currently underused. Most applied radiation doses range from 12 Gy up to 21 Gy, however, the best radiation dose to palliate dysphagia remains uncertain. In addition, a randomized trial from the Netherlands compared stent placement or single-dose (12 Gy) radiotherapy in inoperable esophageal cancer patients with dysphagia (Homs 2004). This study showed rapidly improved dysphagia after stent placement compared to brachytherapy, however, long-term relief of dysphagia was better after brachytherapy and also was associated with less complications (33% vs. 21%; $p = 0.02$). No difference was seen in persistent or recurrence dysphagia or median survival between both groups. The authors therefore conclude that brachytherapy should be considered as primary treatment for palliation of dysphagia in patients with an expected survival of more than three months. Despite the benefits of brachytherapy, there are pitfalls too including the risk of esophagitis, stricture and fistula as well as patients' commitment to multiple treatments. In the future, results from a large multicenter prospective study comparing external-beam and intraluminal radiotherapy are expected.

Best Supportive Care

The decision to offer palliative therapy or best supportive care could depend on the patient's performance status according to the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) or the Karnofsky Performance Status Scale

(KPS). Best supportive care is focused on preventing or relieving symptoms instead of trying to cure esophageal cancer or to prolong life. In case of pain or physical discomfort, analgesics could be used. If food passage through the esophagus is no longer possible due to progressive disease in patients with short life expectancy, food intake could be restored by placement of an esophageal stent. For palliation of malignant dysphagia fully or partially covered expandable metal stents made of nitinol are recommended and can be placed across the length of the tumor using endoscopy. Although its fast improvement of dysphagia symptoms, it can also lead to symptoms such as reflux and chest pain.

Summary

1. The aim of palliative chemotherapy is to prolong survival and maintain quality of life, but its benefit is limited.
2. First-line, second-line and third-line therapy could consist of combined chemotherapeutic agents, chemotherapy plus PD-1 inhibitors/epidermal growth factor receptor or combined immunotherapeutic agents.
3. Palliative radiotherapy alone could be considered in patients not fit for surgery and can be useful to relief symptoms as dysphagia and pain.
4. Best supportive care, including esophageal stenting or analgesics are used to prevent or relieve symptoms instead of cure esophageal cancer or prolong life.

Section 9 Targeted Therapy and Immunotherapy

Targeted Therapy

With the identification of new biomarkers for esophageal cancers (EC), targeted therapies are gaining interest. Potentially targetable pathways in EC includes human epidermal growth factor receptor 2 (HER2, Neu, ErbB2), the epidermal growth factor receptor (EGFR, Her1, ErbB1), the vascular endothelial growth factor (VEGF) and the mesenchymal-epithelial transition (MET) factor (Table 8).

HER2

HER2 is a tyrosine kinase that localizes to the cell membrane and conducts extracellular-intracellular signaling to regulate cell growth and differentiation, as well as the development of cancer. For adenocarcinoma, trastuzumab is the primary therapeutic drug targeting HER2 and part of the standard first-line treatment for HER2-positive gastroesophageal junction (GEJ). In the phase III JACOB trial, another HER2 targeted agent pertuzumab was added to trastuzumab plus chemotherapy for the treatment of metastatic HER2-postive adenocarcinoma of the GEJ or stomach and in a Chinese and Japanese subpopulation analysis of this trial, overall survival was

Table 8 Clinical trials of targeted therapies for ESCC.

First author	Type of study	Study population	Targeted therapy	In combination with	Results
HER					
Guo (Guo 2018)	Lapatinib	/	Preclinical	Paclitaxel	Synergistic antitumor activity
EGFR					
Zhang (Zhang 2019)	Nimotuzumab	Metastatic ESCC (Fist line)	Phase II	Paclitaxel and Cisplatin	Median PFS 6.6–18.1mo MST 11.5–26.2mo
Xu (Xu 2016)	Gefitinib	ESCC (Second line)	Phase II	None	Median PFS 2.2 mo MST 6.1 mo
Huang (Huang 2016)	Icotinib	ESCC	Phase II	/	Median PFS 52 days MST 153 days
VEGF/VEGFR					
Chang (Chang 2013)	Endostar	/	Preclinical	Paclitaxel + Cisplatin	Inhibitory effect on ESCC
Li (Li 2019)	Apatinib	ESCC	Phase II	Docetaxel	Median PFS 175 days
Huang (Huang 2021)	Anlotinib	ESCC (second line)	Phase II	None	Median PFS 3.02 mo

Abbreviations: ESCC: Esophageal squamous cell carcinoma; PFS: Progression free survival; MST: Median survival time.

numerically but not statistical significantly improved by addition of pertuzumab. The same evidence for ESCC, however, has not been established. Lapatinib on the other hand, a small-molecule inhibitor of EGFR and HER2, was proven to have highly synergistic effect on inhibiting cell proliferation in vitro and significantly reduced the invasion and migration of ESCC cells in combination with paclitaxel (Guo 2018). The clinical evidence of HER2's role in patients with ESCC is yet to be explored.

EGFR

EGFR (Her1, ErbB1) is a receptor tyrosine kinase that belongs to the ErbB family which includes three other members (ErbB2/HER2/Neu, ErbB3/HER3, and ErbB4/HER4). Activation of EGFR leads to phosphorylation of the receptor which then activates several downstream effectors, such as the RAS-RAF-MEK-ERK-MAPK and the PI3K- AKT-mTOR pathways. In EC, the efficacy of EGFR inhibitors is precluded to those patients whose tumor is KRAS wild type, as tumors with a gain-of-function KRAS mutations have a constitutively active pathway downstream of EGFR. An FDA approved anti-EGFR agent is cetuximab, used to treat patients with advanced metastatic colorectal cancer. Several studies suggested that adding cetuximab to other treatments (such as radiotherapy or chemotherapy) can improve survival outcomes in ESCC. (For details see previous Section First-line treatment.) Nimotuzumab, on the other hand, is a fully recombinant, humanized monoclonal antibody against EGFR. It is the first monoclonal antibody in China used to treat malignant tumors, such as head and neck cancers. In comparison with conventional chemotherapy, nimotuzumab achieved significant anticancer effect with tolerable toxicity for metastatic ESCC (Zhang 2019). The same limited evidence of potential treatments for ESCC has been found for gefitinib and icotinib, both showed promising results in phase II trials (Xu 2016) (Huang 2016). Although EGFR inhibitors could develop into a vital candidate for treating ESCC, further research on the clinical implications are needed.

VEGF

As regulators of angiogenesis, VEGFs play an important role in the proliferation and angiogenesis of vascular endothelial cells. The evidence of the efficacy of well-known VEGF inhibiting agents such as bevacizumab and ramucirumab are limited to patients with EAC or GEJ. Targeting ESCC, Chinese scientists developed a novel recombinant human endostatin Endostar, which has found effective in suppressing angiogenesis and tumor growth. Endostar has been approved by the China Food and Drug Administration (CFDA) for use with cisplatin or other chemotherapy drugs to treat small cell lung cancer, but effects on ESCC have only been studied in animal models (Chang 2013). Apatinib and anlotinib, both with VEGFR inhibition effects, have undergone phase II trials showing beneficial effects on progression free survival. Anlotinib monotherapy was included in the 2019 version of the Chinese Society of Clinical Oncology (CSCO) – EC guidelines as a second-line and beyond treatment for ESCC (Li 2019) (Huang 2021).

MET

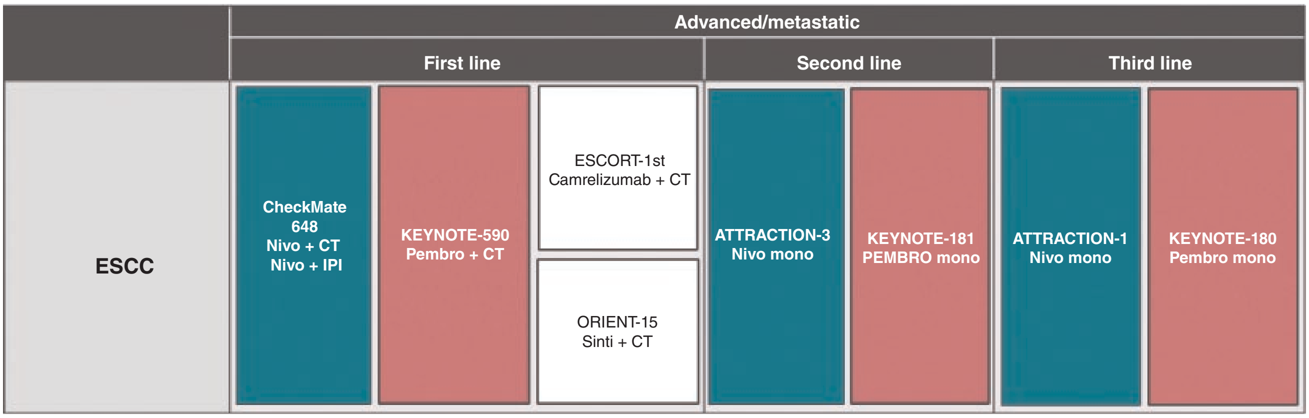
The tyrosine protein kinase MET is a receptor for the hepatocyte growth factor (HGF) and interaction between those two leads to tumor cell growth, invasion and metastasis. Agents such as AMG102, AMG331 and Onartuzumab failed to demonstrate any survival benefits in EC patients, but further research is required to better elucidate which patient populations may potentially benefit from this therapy.

Immunotherapy

Diagnosis of ESCC typically occurs in patients with locally advanced unresectable or metastatic disease, when palliative chemotherapy is the primary treatment option, but five-year survival rates can be as low as 5%. Better systemic therapies are an urgent call in the treatment landscape of ESCC. Immunotherapy is a strategy to enhance the efficacy and specificity of the immune cells to suppress cancer progression (Figure 9). In the treatment of EC, immune checkpoint inhibitors which can bind to protein receptors on the surface of T cells or tumor cells to prevent tumor cells from immune escape, is a hot research area. The programmed cell death protein 1 (PD-1) pathway is considered one such important inhibitory mechanism and programmed cell death-ligand 1 (PD-L1) inhibitors are considered effective drugs to address cancer cell evasion of T cells.

Camrelizumab (See First Line Therapy in Section 8)

Camrelizumab is a humanized anti-PD-1 monoclonal antibody independently developed in China. One of the pivotal trials is the KEYNOTE-590 trial, which is a randomized phase-III study investigating first-line chemotherapy with or without pembrolizumab for advanced unresectable or metastatic esophageal cancer. The phase-III ESCORT-1st study investigated the efficacy and safety of camrelizumab plus chemotherapy vs. chemotherapy alone in patients with untreated advanced or metastatic ESCC. The survival benefit was revealed across all strata, irrespective of programmed cell death ligand 1 (PD-L1) expression.



	Advanced/metastatic						
	First line			Second line		Third line	
ESCC	CheckMate 648 Nivo + CT Nivo + IPI	KEYNOTE-590 Pembro + CT	ESCORT-1st Camrelizumab + CT ORIENT-15 Sinti + CT	ATTRACTION-3 Nivo mono	KEYNOTE-181 PEMBRO mono	ATTRACTION-1 Nivo mono	KEYNOTE-180 Pembro mono

Figure 9 Summary of immunotherapy treatment trials for ESCC. *Abbreviation: Nivo=Nivolumab; CT=Chemotherapy; IPI=Ipilimumab; Mono=Monotherapy; Sinti=Sintilimab; Pembro=Pembrolizumab.*

Pembrolizumab (See Second Line Therapy in Section 8)

Pembrolizumab is approved by the FDA for the treatment as a second line option for PD-L1 positive ESCC, based on the KEYNOTE-180 phase II and KEYNOTE-181 phase III trials. In the first-line setting, the addition of pembrolizumab to chemotherapy was investigated in the KEYNOTE-590 trial, in which 73% of the patients had ESCC. This trial demonstrated that the addition of pembrolizumab to chemotherapy in this group prolonged overall survival in all subgroups, but this was most pronounced in the PD-L1 CPS >10 group (from 8.8 to 13.9 months). In Europe, the EMA has registered pembrolizumab for this PD-L1 high subgroup only.

Nivolumab (See Palliative Treatment in Section 8 and Adjuvant Therapy in Section 7)

Nivolumab has been approved for a variety of metastatic or locally advanced tumors, including ESCC. In the phase III CheckMate 648 trial focused on ESCC, the overall survival advantage with nivolumab plus chemotherapy vs chemotherapy alone was 15.4 vs. 9.1 months in patients with tumor-cell PD-L1 expression of 1 or greater. In all randomized patients, the beneficial effect of nivolumab was less pronounced (13.2 vs 10.7 months). A third group receiving only nivolumab plus ipilimumab (dual checkpoint inhibition) had likewise favorable results, but was not directly compared to the chemotherapy plus nivolumab arm. In patients with a specific contra-indication for chemotherapy but overall good performance, this does give the option of a chemotherapy-free treatment. Moreover, nivolumab administered as adjuvant treatment following neoadjuvant chemoradiation and complete surgical resection in patients with esophageal or GE junction cancer without pathological complete response, demonstrated statistically significant improvement in disease-free survival (DFS) in the phase III CheckMate-577 trial with a doubling of DFS from 11 to 22 months.

Immune checkpoint inhibitors (in combination with chemotherapy), and even dual checkpoint inhibition, will become a feasible option for many patients with ESCC worldwide. Nevertheless, besides the challenge of selecting the patients most likely to benefit from immunotherapy approaches, it will be paramount to tackle issues of access, especially in low-resource settings.

Summary

1 The evidence for targeted therapies in treating ESCC is limited to results from phase II trials.
2 Immune checkpoint inhibitors will likely become a feasible option for many patients with ESCC worldwide.

Section 10 Recent and Future Developments

Neoadjuvant Immunotherapy

The benefit of neoadjuvant immunotherapy is that this may induce tumor shrinkage and facilitate a radical resection of the tumor. Shen et al. administered 28 patients with resectable locally advanced ESCC to evaluate the feasibility and safety of a neoadjuvant treatment protocol of PD-1 inhibitors (pembrolizumab: 2 mg/kg, nivolumab: 3 mg, camrelizumab: 200 mg) combined with nCT (albumin paclitaxel + carboplatin). This regimen produced an unprecedentedly high R0 resection and pathologically complete response rates (pCR). (Shen 2021). The Palace-1 study included 20 resectable ESCC patients to receive preoperative pembrolizumab with concurrent carboplatin, paclitaxel, and radiotherapy. Grade III and higher adverse events were observed in 65% of the patients and the pCR rate was 55.6%. Despite these positive findings, it is still uncertain what the optimum number of neoadjuvant therapy cycles is and no phase-3 trial has been completed yet (Shen 2021).

Robot-assisted Minimally Invasive Esophagectomy (RAMIE)

The introduction of RAMIE is one of the most important developments on surgical techniques in the past 10 years. Robotic assistance allows for more natural hand movements and provides an enhanced three-dimensional vision of the surgical field. The evidence of superiority of RAMIE over other techniques is limited yet. However, a reduction in pulmonary complications is seen over open approach as has been reported for other minimally invasive approaches. Tumor RAMIE is safe and an alternative to open esophagectomy (van der Sluis et al. 2012). The long term results and the possible benefits over minimally invasive techniques still are unclear (Tagkalos 2021).

Since metastases to upper mediastinal nodes are commonly seen in ESCC, lymph node dissection along the bilateral recurrent laryngeal nerve (RLN) may become easier with RAMIE and reduce post-procedural morbidity. A multicenter randomized trial randomized trial – termed REVATE – is currently ongoing with the aim of comparing the rates of successful RLN nodal dissection during RAMIE *versus* MIE.

Surgery as Needed

The CROSS trial showed a pathologically complete response (pCR) in the resection specimen in 49% of patients with squamous cell carcinoma after neoadjuvant chemoradiotherapy (Van Hagen 2012). This high pCR rate raises the question if surgical resection is of benefit to these patients or if patients already were cured locoregionally by neoadjuvant treatment alone. Theoretically, an organ sparing approach might be feasible as esophagectomy in patients with no residual disease likely does not change the outcome. Surgery is associated with considerable perioperative morbidity and reduces quality of life in the short and long term. Therefore, if one could identify patients with a clinically complete response after neoadjuvant chemoradiotherapy, applying active surveillance in these patients may be a realistic option. The preSANO trial revealed that the combination of endoscopic bite-on-bite biopsies, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) of suspected lymph nodes and 18F-FDG PET-CT had a sensitivity of 90% to detect TRG3-4 residual tumors (>10% residual tumor cells) (Noordman et al. 2018a). This combination of diagnostic modalities is now being used in a phase-III randomized controlled trial (SANO-trial). The SANO-trial investigates whether an active surveillance strategy is non-inferior to standard surgery after neoadjuvant chemoradiotherapy (Eyck et al. 2021a; Noordman et al. 2018b). The first results of this trial are expected in late-2023. A recent meta-analysis of seven cohort studies showed that overall survival between patients undergoing standard surgery or active surveillance after neoadjuvant chemoradiotherapy is comparable (Van der Wilk 2022). This may support offering active surveillance as an alternative treatment strategy, but this study has several shortcomings. The study included predominantly retrospective studies with small sample sizes and patients included in active surveillance from these studies are likely highly selected and as such may represent a subgroup with a more favorable prognosis.

Based on the diagnostic modalities used in the preSANO trial, a prospective multicenter study (preSINO trial) is recruiting patients with esophageal squamous cell carcinoma in order to assess the accuracy of response evaluation after neoadjuvant chemoradiotherapy in the eastern population (Zhang 2020). In France also, a current study on active surveillance is performed (Esostrate trial) which enrolls both esophageal SCC and adenocarcinoma. A lot of research is being done into organ-sparing treatment for esophageal cancer whose results are still awaited.

Key Take Home Messages

- Advanced endoscopic imaging has shown promising results in the detection of early cancerous lesions. Existing screening programs are however limited to high-risk Chinese populations.
- Routine clinical staging of esophageal cancer includes upper endoscopy with biopsies, endoscopic ultrasonography with fine-needle aspiration and ^{18}F-FDG PET/CT and on indication bronchoscopy EBUS, MRI-scan or diagnostic laparoscopy/thoracoscopy.
- The precursor of ESCC is squamous dysplasia and is commonly divided into low- and high- grade dysplasia. ESCC is divided into well, moderately and poorly differentiated.
- The 8th edition of UICC/AJCC TNM and the Japanese classification system JES are used for pathological staging of ESCC. The Japanese classification differs in lymph node mapping as this is based on location of lymph nodes according to tumor location.
- Endoscopic resection is the standard treatment for intramucosal ESCC. Adjuvant therapy may be needed in tumors with unfavorable pathological characteristics and for incomplete resections.
- Patients with cT1-2 ESCC without lymph node metastases qualify for immediate surgery according to Asian guidelines.

A transthoracic esophagectomy with two- or three field nodal dissection is standard treatment.

- Preoperative treatment for SCC in the West preferably consists of chemoradiotherapy, while Eastern countries may prefer chemotherapy or adjuvant therapy.
- Definitive chemoradiation is an alternative treatment for SCC and treatment of choice for irresectable (T4b) SCC or for patients unfit for surgery.
- There has been a shift in the treatment of adjuvant or metastatic esophageal cancer toward chemotherapy combined with immunotherapy, including PD-1 inhibitors, epidermal growth factor receptor and targeted therapies.

Knowledge Gaps

- Cytology and serum blood-markers appear as a promising non-invasive test for (early) disease detection for ESCC, but further investigations are required to assess clinical applicability.
- Indications for adjuvant systematic therapy or resection after endoscopic resection for ESCC are inconsistent.
- The extent of lymph node dissection during esophagectomy differs in Eastern and Western practices and its therapeutic benefit is still debated.
- Guidelines are not unequivocal about the use, optimal dose of radiation and choice of chemotherapeutic agents for definitive chemoradiotherapy. This needs to be further examined.
- Proton-based radiation (in combination with chemotherapy) is promising, but more research need to be done to evaluate its benefit compared to standard photon-based radiation.
- The role of neoadjuvant immunotherapy is promising but no phase-3 trial has been completed yet.
- In patients with a locoregional complete clinical response to neoadjuvant treatment may undergo active surveillance (i.e. surgery as needed) could be of benefit. However, results of prospective trials (SANO trial, Esostrate) should be awaited before waiving standard esophagectomy after neoadjuvant therapy can be discussed.

(Inter)national Evidence-based Websites

- National Cancer Institute
  https://www.cancer.gov/types/esophageal
- The Japan Esophageal society
  https://www.esophagus.jp/global
- National Comprehensive Cancer Network
  https://www.nccn.org/home
- European Society for Medical Oncology
  https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/oesophageal-cancer
- UpToDate
  https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-staging-of-esophageal-cancer

References

Ajani, J.A. (2012). Preoperative chemotherapy for localized squamous cell carcinoma of the esophagus? We should go back to the drawing board! *Ann Surg Oncol* 19: 3–4.

Ajani, J.A. (2019). Esophageal and esophagogastric junction cancers, Version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 17: 855–883.

Akiyama, H. (1994). Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 220: 364–372.

Allum, W. (2002). Guidelines for the management of oesophageal and gastric cancer. *Gut* 50 (Suppl 5): v1–23.

Allum, W. (2011). Guidelines for the management of oesophageal and gastric cancer. *Gut* 60: 1449–1472.

Ando, N. (2012). A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 19: 68–74.

Arnal, M.J.D. (2015). Esophageal cancer: risk factors, screening and endoscopic treatment in Western and Eastern countries. *World J Gastroenterol* 21: 7933.

Barreto, J.C. (2010). Transhiatal versus transthoracic esophagectomy for esophageal cancer. *World J Gastroenterol* 16: 3804.

Becker, K. (2003). Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer* 98: 1521–1530.

Biere, S.S. (2012). Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 379: 1887–1892.

Bleiberg, H. (1997). Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer* 33: 1216–1220.

Borggreve, A.S. (2018). Surgical treatment of esophageal cancer in the era of multimodality management. *Ann N Y Acad Sci* 1434: 192–209.

Bosset, J.F. (1997). Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 337: 161–167.

Bray, F. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68: 394–424.

Cao, X.F. (2009). Effects of neoadjuvant radiochemotherapy on pathological staging and prognosis for locally advanced esophageal squamous cell carcinoma. *Dis Esophagus* 22: 477–481.

Carreiro, A. (2013). Bronchoscopy and esophageal cancer. *Eur Respir J* 42: P3778.

Cavallin, F. (2018). Esophageal cancer clinical presentation: trends in the last 3 decades in a large Italian series. *Ann Surg* 267: 99–104.

Chang, L. (2013). The inhibitory effects of Endostar combined with chemotherapy on human esophageal squamous cell carcinoma xenograft in mice. *Mol Biol Rep* 40: 669–673.

Chen R., Liu Y., Song G., Li B. (2021). Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. *Gut* 70 (2): 251–260.

doi:10.1136/gutjnl-2019-320200. Epub 2020 Apr 2. PMID: 32241902; PMCID: PMC7815635.

Cooper, J.S. (1999). Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation therapy oncology group. *JAMA* 281: 1623–1627.

D'Amico, T.A. (2014). Mckeown esophagogastrectomy. *J Thorac Dis* 6 (Suppl 3): S322–4.

Doki, Y. (2022). Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med* 386: 449–462.

Dutton, S.J. (2014). Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 15: 894–904.

Esposito, V.R. (2020). Resection of the irradiated esophagus: the impact of lymph node yield on survival. *Dis Esophagus* 33.

Eyck, B.M. (2021a). Updated protocol of the SANO trial: a stepped-wedge cluster randomised trial comparing surgery with active surveillance after neoadjuvant chemoradiotherapy for oesophageal cancer. *Trials* 22: 345.

Eyck, B.M. (2021b). Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: the randomized controlled CROSS trial: 2021. *J Clin Oncol* 39: 1995–2004.

Fuccio, L. (2017). Brachytherapy for the palliation of dysphagia owing to esophageal cancer: a systematic review and meta-analysis of prospective studies. *Radiother Oncol* 122: 332–339.

Fujishiro M, K.S. (2009). Indications, techniques, and outcomes of endoscopic submucosal dissection for esophageal squamous cell carcinoma. *Esophagus* 6: 143–148.

Gibson, M. (2022) Epidemiology and pathobiology of esophageal cancer. UpToDate. available from: https://www.uptodate.com/contents/epidemiology-and-pathobiology-of-esophageal-cancer [online]. Accessed May 1st, 2022.

Gotink, A.W. (2017). Exploring diagnostic and therapeutic implications of endoscopic mucosal resection in EUS-staged T2 esophageal adenocarcinoma. *Endoscopy* 49: 941–948.

Guo, X. (2018). "Lapatinib in combination with paclitaxel plays synergistic antitumor effects on esophageal squamous cancer. *Cancer Chemother Pharmacol* 82 (3): 383–394.

Hikichi, T. (2020). Prevention of stricture after endoscopic submucosal dissection for superficial esophageal cancer: a review of the literature. *J Clin Med* 10: 20.

Homs, M.Y. (2004). Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet* 364: 1497–1504.

Huang, J. (2016). Icotinib in patients with pretreated advanced esophageal squamous cell carcinoma with EGFR overexpression or EGFR gene amplification: a single-arm, multicenter phase 2 study. *J Thorac Oncol* 11: 910–917.

Huang, J. (2021). Anlotinib for previously treated advanced or metastatic esophageal squamous cell carcinoma: a double-blind randomized phase 2 trial. *Cancer Med* 10 (5): 1681–1689.

Hulshof, M. (2021). Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO study): 2021. *J Clin Oncol* 39: 2816–2824.

James, D.B. (2017). *TNM Classification of Malignant Tumours*. Chichester, West Sussex, UK: Wiley-Blackwell.

Janmaat, V.T. (2017). Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer: 2017. *Cochrane Database Syst Rev* 11: CD004063.

Japanese Esophageal Society (2017). Japanese classification of esophageal cancer, 11th Edition: part I. *Esophagus* 14: p1–36.

Jeene, P.M. (2018). The role of definitive chemoradiation in patients with non-metastatic oesophageal cancer. *Best Pract Res Clin Gastroenterol* 36–37: 53–59.

Jeene, P.M. (2020). Short-course external beam radiotherapy versus brachytherapy for palliation of dysphagia in esophageal cancer: a matched comparison of two prospective trials. *J Thor Oncol* 15: 1361–1368.

Kato, H. (2005). The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. *Cancer* 103: 148–156.

Kato, K. (2019). Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial". *Lancet Oncol* 20: 1506–1517.

Kato, K. (2021). Parallel-Group controlled trial of surgery versus chemoradiotherapy in patients with stage I Esophageal squamous cell carcinoma. *Gastroenterology* 161: 1878–1886.e2.

Kelly, R.J. (2021). Adjuvant Nivolumab in resected Esophageal or Gastroesophageal junction cancer. *New Engl J Med* 384 (13): 1191–1203.

Ken, K. (2021). Nivolumab in advanced esophageal squamous cell carcinoma (ATTRACTION-1/ONO-4538-07): minimum of five-year follow-up. *J Clin Oncol* 39: 207-207.

Ken, K. (2022). A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study. *J Clin Oncol* 40: 238–238.

Kim, T.J. (2009). Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. *Radiographics* 29: 403–421.

Kitagawa, Y. (2019). Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal society: part 1. *Esophagus* 16: 1–24.

Kohli, D. (2017). Performance characteristics of optical coherence tomography in assessment of Barrett's esophagus and esophageal cancer: systematic review. *Dis Esophagus* 30: 1–8.

Kojima, T. (2020). Randomized phase III KEYNOTE-181 study of Pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol* 38: 4138–4148.

Kumarasinghe, M.P. (2020). Pathological assessment of endoscopic resections of the gastrointestinal tract: a comprehensive clinicopathologic review. *Mod Path* 33 (6): 986–1006.

Lagarde, S.M. (2008). Preoperative prediction of the occurrence and severity of complications after esophagectomy for cancer with use of a nomogram. *Ann Thorac Surg* 85: 1938–1945.

Lee, J.L. (2004). A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. *Ann Oncol* 15: 947–954.

Lee, S.L. (2021). Diagnostic performance of MRI for esophageal carcinoma: a systematic review and meta-analysis. *Radiology* 299: 583–594.

Levard, H. (1998). 5-Fluorouracil and cisplatin as palliative treatment of advanced oesophageal squamous cell carcinoma. A multicentre randomised controlled trial. The French associations for surgical research. *Eur J Surg* 164: 849–857.

Lewis, I. (1946). The surgical treatment of carcinoma of the oesophagus; with special reference to a new operation for growths of the middle third. *Br J Surg* 34: 18–31.

Li, J. (2019). Clinical efficacy and survival analysis of apatinib combined with docetaxel in advanced esophageal cancer. *Onco Targ ther* 12: 2577–2583.

Lin, S.H. (2020). Randomized phase IIB trial of proton beam therapy versus intensity-modulated radiation therapy for locally advanced esophageal cancer. *J Clin Oncol* 38: 1569–1579.

Liu, Z. (2021). Additional esophagectomy following noncurative endoscopic resection for early esophageal squamous cell carcinoma: a multicenter retrospective study. *Ann Surg Oncol* 28: 7149–7159.

Lordick, F. (2016). Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27: v50–v57.

Lorenzen, S. (2009). Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie". *Ann Oncol* 20: 1667–1673.

Low, D.E. (2015). International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy complications consensus group (ECCG). *Ann Surg* 262: 286–294.

Mandard, A.M. (1994). Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. *Cancer* 73: 2680–2686.

Marginean, E.C. (2020). Pathologic assessment of endoscopic resection specimens with superficial carcinoma of the esophagus: current practice and practical issues. *Ann N Y Acad Sci* 1482 (1): 130–145.

Mariette, C. (2019). Hybrid minimally invasive esophagectomy for esophageal cancer. *New Engl J Med* 380: 152–162.

Matsuda, S. (2017). Three-field lymph node dissection in esophageal cancer surgery. *J Thorac Dis* 9: S731–S740.

Minashi, K. (2019). Efficacy of endoscopic resection and selective chemoradiotherapy for stage I Esophageal squamous cell carcinoma. *Gastroenterology* 157 (382–390.e3).

Minsky, B.D. (2002). INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 20: 1167–1174.

Miyazaki, T. (2014). Effectiveness of FDG-PET in screening of synchronous cancer of other organs in patients with esophageal cancer". *Anticancer Res* 34: 283–287.

Moehler, M. (2020). Cisplatin and 5-fluorouracil with or without epidermal growth factor receptor inhibition panitumumab for patients with non-resectable, advanced or metastatic oesophageal squamous cell cancer: a prospective, open-label, randomised phase III AIO/EORTC trial (POWER). *Ann Oncol* 31: 228–235.

Morita, F.H. (2017). Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. *BMC Cancer* 17: 54.

Murray, L.J. (2012). Palliative radiotherapy in patients with esophageal carcinoma: a retrospective review. *Pract Radiat Oncol* 2: 257–264.

Nienhueser, H. (2015). Surgery of gastric cancer and esophageal cancer: does age matter? *J Surg Oncol* 112: 387–395.

Noordman, B.J. (2018a). Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. *Lancet Oncol* 19: 965–974.

Noordman, B.J. (2018b). Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. *BMC Cancer* 18: 142.

Noordzij, I.C. (2019). Endoscopic resection for early esophageal carcinoma. *J Thor Dis* 11: S713–S722.

Omloo, J.M. (2008). Value of bronchoscopy after EUS in the preoperative assessment of patients with esophageal cancer at or above the carina. *J Gastrointest Surg* 12: 1874–1879.

Pech, O. (2014). Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology* 146 (652–660): e1.

Penniment, M.G. (2018). Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). *Lancet Gastroenterol Hepatol* 3: 114–124.

Petty, R.D. (2017). Gefitinib and EGFR gene copy number aberrations in esophageal cancer. *J Clin Oncol* 35: 2279–2287.

Polee, M.B. (2002). Phase II study of bi-weekly administration of paclitaxel and cisplatin in patients with advanced oesophageal cancer". *Br J Cancer* 86: 669–673.

Polee, M.B. (2004). A phase I and pharmacokinetic study of weekly paclitaxel and carboplatin in patients with metastatic esophageal cancer. *Clin Cancer Res* 10: 1928–1934.

Puli, S.R. (2008). Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. *World J Gastroenterol* 14: 1479–1490.

Quint, L.E. (2008). Staging esophageal cancer. *Cancer Imag* 8 Spec No A, S33–42.

Rice, T.W. (2016a). Worldwide Esophageal cancer collaboration: pathologic staging data. *Dis Esophagus* 29: 724–733.

Rice, T.W. (2016b). Worldwide Esophageal cancer collaboration: neoadjuvant pathologic staging data. *Dis Esophagus* 29: 715–723.

Rice, T.W. (2017). 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* 6: 119–130.

Riedel, M. (2000). Predictors of tracheobronchial invasion of suprabifurcal oesophageal cancer. *Respiration* 67: 630–637.

Rui-Hua, X. (2021). ESCORT-1st: a randomized, double-blind, placebo-controlled, phase 3 trial of camrelizumab plus chemotherapy versus chemotherapy in patients with untreated advanced or metastatic esophageal squamous cell carcinoma (ESCC). *J Clin Oncol* 39: 4000-4000.

Rustgi, A.K. (2014). Esophageal carcinoma. *N Engl J Med* 371: 2499–2509.

Saliba, G. (2021). Tumor regression grading after neoadjuvant treatment of esophageal and gastroesophageal junction adenocarcinoma: results of an international Delphi consensus survey. *Human Pathol* 108: 60–67.

Schatz, R.A. (2017). Gastrointestinal bleeding due to gastrointestinal tract malignancy: natural history, management, and outcomes. *Dig Dis Sci* 62: 491–501.

Shah, M.A. (2019). Efficacy and safety of Pembrolizumab for heavily pretreated patients with advanced, metastatic Adenocarcinoma or Squamous cell carcinoma of the Esophagus: the phase 2 KEYNOTE-180 study. *JAMA Oncol* 5: 546–550.

Shah, M.A. (2020). Treatment of locally advanced esophageal carcinoma: ASCO guideline. *J Clin Oncol* 38: 2677–2694.

Shen, L. (2021). LBA52 Sintilimab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced or metastatic esophageal squamous cell cancer: first results of the phase III ORIENT-15 study". *Ann Oncol* 32: S1330.

Sun, J.M. (2021). Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 398: 759–771.

Tagkalos, E. (2021). Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus minimally invasive esophagectomy for resectable esophageal adenocarcinoma, a randomized controlled trial (ROBOT-2 trial). *BMC Cancer* 21.

Takahashi, C. (2021). Comparative outcomes of transthoracic versus transhiatal esophagectomy. *Surgery* 170: 263–270.

Taylor, P.R. (2013). Squamous Dysplasia—The precursor lesion for esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 22: 540–552.

Udagawa, H. (2012). The importance of grouping of lymph node stations and rationale of three-field lymphoadenectomy for thoracic esophageal cancer. *J Surg Oncol* 106: 742–747.

Udagawa, H. (2018). Comparison of two major staging systems of esophageal cancer-toward more practical common scale for tumor staging. *Ann Transl Med* 6: 76.

Van der Sluis, P.C. (2019). Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. *Ann Surg* 269: 621–630.

van der Sluis P.C., Ruurda J.P., van der Horst S. et al. (2012). Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer, a randomized controlled trial (ROBOT trial). *Trials* 2012 Nov 30;13: 230. doi:10.1186/1745-6215-13-230 PMID: 23199187; PMCID: PMC3564860.

Van der Wilk, B.J. (2022). Chemoradiotherapy followed by active surveillance versus standard esophagectomy for esophageal cancer: a systematic review and individual patient data meta-analysis. *Ann Surg* 275: 467–476.

Van Hagen, P. (2012). Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 366: 2074–2084.

Van Westreenen, H.L. (2004). Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol* 22: 3805–3812.

Van Workum, F. (2021). Intrathoracic vs cervical anastomosis after totally or hybrid minimally invasive esophagectomy for esophageal cancer. *JAMA Surg* 156: 601.

Visaggi, P. (2021). Modern diagnosis of early esophageal cancer: from blood biomarkers to advanced endoscopy and artificial intelligence. *Cancers* 13: 3162.

Visser, E. (2019). Prognostic value of Lymph Node Yield on overall survival in Esophageal cancer patients: a systematic review and meta-analysis. *Ann Surg* 269: 261–268.

Wang, G.Q. (2005a). Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. *Gut* 54: 187–192.

Wang, H. (2021). Morbidity and mortality of patients who underwent minimally invasive esophagectomy after neoadjuvant chemoradiotherapy vs neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: a randomized clinical trial. *JAMA Surg* 156: 444–451.

Wang, L.D. (2005b). Cytological screening and 15 years' follow-up (1986-2001) for early esophageal squamous cell carcinoma and precancerous lesions in a high-risk population in Anyang County, Henan Province, Northern China. *Cancer Detect Prev* 29: 317–322.

Wei, Y. (2017). Esophageal carcinoma: ex vivo evaluation by high-spatial-resolution T(2) -mapping MRI compared with histopathological findings at 3.0T. *J Magn Reson Imaging* 45: 1609–1616.

WHO Editorial Board (2019). Digestive system tumours, WHO classification of tumours. 5e.

Wilson, G.D. (2006). Biologic basis for combining drugs with radiation. *Semin Radiat Oncol* 16: 2–9.

Xu, Y. (2016). Gefitinib single drug in treatment of advanced esophageal cancer. *J Cancer Res Ther* 12 (Supplement): C295–C297.

Yamada, I. (2014). Esophageal carcinoma: ex vivo evaluation with diffusion-tensor MR imaging and tractography at 7 T. *Radiology* 272: 164–173.

Yang, H. (2018). Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell Carcinoma of the Esophagus (NEOCRTEC5010): a Phase III multicenter, randomized, open-label clinical trial. *J Clin Oncol* 36: 2796–2803.

Zhang, S.S. (2014). Adjuvant chemotherapy versus surgery alone for esophageal squamous cell carcinoma: a meta-analysis of randomized controlled trials and nonrandomized studies. *Dis Esophagus* 27: 574–584.

Zhang, X. (2019). Nimotuzumab Plus Paclitaxel and Cisplatin as a 1st-Line treatment for Esophageal cancer: long term follow-up of a phase II study. *J Cancer* 10 (6): 1409–1416.

Zhang, X. (2020). Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma (preSINO trial): a prospective multicenter diagnostic cohort study. *BMC Cancer* 20: 194.

6 Management of Diffuse Gastric Cancer

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Introduction

Gastric cancer is among the top four leading causes of cancer-related deaths worldwide. Gastric cancer is histologically divided into intestinal and diffuse type (Lauren 1965). The incidence of intestinal-type gastric cancer has decreased in the last few decades, however the incidence of diffuse type gastric cancer (DGC) continues to be unchanged (Henson et al. 2004; van Der Kaaij et al. 2020). Gastric cancer can be further divided into sporadic or inherited. Inherited gastric cancer is attributed to high-risk mutations which have only been identified for the diffuse histotype which is hereditary diffuse gastric cancer (Chen et al. 2016; Petrelli et al. 2017). HDGC is a rare syndrome characterized by autosomal dominant inheritance with high penetrance. The subtypes of gastric cancer have different modes of dissemination patterns: intestinal gastric cancer generally disseminates hematogenously to the liver, while diffuse gastric cancer spreads via the peritoneal surface (Garcia-Pelaez et al. 2021). This classification is of importance because it determines the phenotypic nature as well as the prognosis. The survival rate of DGC is poor, with an average of 18 months (van Der Kaaij et al. 2020) owing to the late stage at diagnosis and poor treatment response.

Hereditary diffuse gastric cancer (HDGC) is characterized by mutations in the tumor suppressor *CDH1* and, to a lesser extent, pathogenic variants of *CTNNA1* gene (Berx et al. 1998). The CDH1 gene is situated on chromosome 16q221 and is made up of 16 exons. It encodes the cell-to-cell adhesion protein E-cadherin (Luo et al. 2018) with germline variants distributed throughout the whole gene (Melo et al. 2017). *CTNNA1* encodes for catenin alpha-1, which is a *CDH-1* binding partner (Benusiglio et al. 2019). The neoplastic process begins with the downregulation of the second copy of the *CDH1* gene or somatic inactivation. Promoter hypermethylation is the most frequent mechanism of biallelic *CDH1* inactivation (Oliveira et al. 2009). *CDH1* genetic variants were discovered as the hallmark of DGC (Cho et al. 2017; Nemtsova et al. 2020; S. C. Wang et al. 2020a). Clinically, the hallmark of HDGC is histologically proven multifocal growth accompanied by signet ring cells in the gastric mucosa as well as lobular breast cancer.

Epidemiology

An estimated 50% of gastric adenocarcinoma are intestinal gastric cancer, and 30% are diffuse gastric cancer, and 15–20% are missed or indeterminate (Iyer et al. 2020). HDGC accounts for 1–3% of all gastric cancer diagnoses (Fitzgerald et al. 2010). The incidence of HDGC is estimated to be 5 in 100,000 persons while the incidence of *CDH1* mutation is estimated to be 1 in 100,000 (Majewski et al. 2013). The *CDH1* mutation was first reported by Yoshiura et al. in 1995 in several types of tumors (Yoshiura et al. 1995). Subsequently in 1998, Guilford identified *CDH1* genetic mutations in a large kindred from New Zealand who had early onset diffuse gastric cancer (Guilford et al. 1998). The incidence of *CDH1* mutation in the Maori population from New Zealand has been reported to be significantly higher. However, precise epidemiological data are still lacking. Additionally, females who harbor a *CDH1* germline pathogenic mutation carry an elevated lifetime risk of 39–52% for Lobular Breast Cancer (LBC) (Hansford et al. 2015). The combined risk of gastric and breast cancer at 80 years of age is approximately 90% (Blair et al. 2020). The median age of diagnosis of HDGC is 38 years (range 14–69 years) (Hansford et al. 2015). An estimated 40% of patients with HDGC have the presence of *CDH1* germline mutation (Hansford et al. 2015), while the *CTNNA1* gene mutation is much less common.

Pathophysiology

Diffuse gastric cancer demonstrates an absence of adhesion molecules, and its hallmark histologically is a poorly differentiated, infiltrative, and poorly cohesive appearance (Iyer et al. 2020). It has been demonstrated that mutations in adhesion and motility protein in diffuse gastric cancer likely contribute to its infiltrative and poorly cohesive histology (Iyer et al. 2020).

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E-cadherin is a type 1-cadherin that is present in the adherens junctions of all epithelial tissues (Yu et al. 2019). It has an extracellular domain, a transmembrane domain, and an intracellular domain. E-cadherin plays an important role in maintaining cell polarity and homeostasis, and cell stability (Maître and Heisenberg 2013). Soluble E-cadherin plays a role in regulating many signaling pathways by both paracrine and autocrine signaling (Kourtidis et al. 2017), thereby modulating signaling pathways such as cylin kinase inhibitor p27-mediated signaling, activation of mitogen-activated kinase (MAPK), rat sarcoma viral oncogene (Ras), phosphatidylinositol-3-kinase (P13K)/AKT, ras-related C3 botulinum toxin substrate (Rac1) signaling and HIPPO signaling and epithelial-mesenchymal transition. Every domain of E-cadherin is susceptible to truncating and missense mutations, with truncation occurring most commonly in EC2, EC3, EC5, and IC (Lo et al. 2019).

The loss of E-cadherin results in weakened adherence junctions in epithelial tissues as well as reduced intercellular stability, which is the first and most important step toward tumorigenesis, metastasis, angiogenesis, and invasion (Goud et al. 2020). E-cadherin is encoded by *CDH1*, and dysregulation results in gastric epithelial cell dysfunction (Liu and Chu 2014). *CDH-1* mutation carriers have a predisposition toward chronic gastritis, foveolar hyperplasia, cystic gland dilatation, and epithelial tufting and globoid changes (Rocha et al. 2018). The most frequently encountered *CDH1* mutations are truncating of deleterious missense mutation, which happens in the cadherin domain (Iyer et al. 2020). *CDH1* mutation carriers are predisposed toward two types of precursor lesions: *in situ* signet-ring carcinoma and the second, which is signet-ring cells with pagetoid growth patterns inside the glandular basal membrane below the non-neoplastic glandular epithelium and foveola (Cosma et al. 2022). While *CDH1* mutations are inherited in an autosomal dominant manner, the penetrance for gastric cancer was shown to be 70% in males and 56% in females (Katona et al. 2020). *TP53* mutation was also discovered to be important to the development of diffuse gastric cancer which is likely to be mutated early in the disease (Iyer et al. 2020).

Diagnosis

Presentation

Diffuse gastric cancer is associated with a poor prognosis due to its aggressive nature as well as late detection of the disease with a poor five-year survival of 45% compared to intestinal gastric cancer at 57.7% (Chen et al. 2016). Symptoms associated with diffuse gastric cancer are vague and can range from asymptomatic to reflux symptoms. Additionally, diffuse gastric cancer may be missed on endoscopy as tumor cells infiltrate in an unpredictable pattern (Kumar et al. 2019; R. Wang et al. 2020a), hence the disease may not be endoscopically visible, and random biopsies of the gastric mucosa may not pick up cells which are too deep or scattered (Iyer et al. 2020). Diffuse gastric cancer has a higher propensity to develop into peritoneal carcinomatosis, which may not be picked up on standard imaging as well as the low standard uptake values (SUV) in PET CT scans likely attributed to a decreased expression of glycolytic pathways compared to intestinal gastric cancer (R. Wang et al. 2020a). In view of the increased propensity for peritoneal metastases in diffuse gastric cancer, diagnostic laparoscopy is a valuable diagnostic tool when clinical suspicion is high in the setting of negative endoscopy (Rawicz-Pruszyński et al. 2019).

Surgical Approaches

Curative surgical management can be performed by total gastrectomy and Roux-en-Y esophagojejunostomy after a baseline endoscopy (Iyer et al. 2020). In the setting of cT1aN0 disease D1 dissection is frequently performed. In patients with cT1N+ and resectable T2–T4 tumors management differs between East Asia and the West. In East Asia, gastrectomy plus D2 dissection is the standard of care. However, D2 dissection did not demonstrate a survival benefit in the West. Therefore, D2 dissection is recommended but not mandatory and should be carried out in a high-volume center by a highly skilled surgeon (Cuschieri et al. 1999; Hartgrink et al. 2004; Mihmanli et al. 2016; Songun et al. 2010). If gastric cancer invades the duodenum then D2 dissection should be extended to encompass the retro-pancreatic lymph nodes with this dissection being termed D2+ (Mihmanli et al. 2016). There is no benefit of D3 dissection as it results in worse survival with associated higher morbidity (Sasako et al. 2008).

Criteria for HDGC Genetic Testing

The International Gastric Cancer Linkage Consortium (IGCLC) has defined the prerequisite in order to guide the clinician to screen for *CDH1/CTNNA1* mutation analysis (Blair et al. 2020). The criteria state that genetic testing for *CDH1* and *CTNNA1* mutations should be performed in a family who has first or second degree relatives who have (1) two or more relatives with gastric cancer regardless of age with at least one having diffuse gastric cancer; (2) one or more relatives with diffuse gastric cancer diagnosed at any age and one or more cases of lobular breast cancer before the age of 70; (3) two or more relatives with lobular breast cancer before the age of 50; meanwhile individual criteria state that (4) diffuse gastric cancer in an individual below the age of 50; (5) gastric *in situ* signet ring cells and/or pagetoid spread of signet ring cells in an individual below the age of 50; (6) diffuse type gastric cancer at age in an individual with personal or first-degree family history of cleft lip or cleft palate; (7) diffuse type gastric cancer and lobular breast cancer in an individual before the age of 70; (8) Bilateral lobular breast cancer or lobular carcinoma *in situ* in an individual diagnosed before the age of 70; (9) Diffuse type of gastric cancer in an individual of Maori ethnicity diagnosed at any age. Genetic testing should be extended to those fulfilling the genetic testing criteria from the legal age of consent from ages 16 to 18 onwards (Blair et al. 2020). Younger individuals may also be offered the test if family history is suggestive (Blair et al. 2020).

Due to the increased risk of gastric cancer, prophylactic gastrectomy is advocated in individuals harboring the *CDH1* mutation and with a history of diffuse gastric cancer in the family (Treese et al. 2022). The recommended age for prophylactic total gastrectomy is from 20 up to approximately 30 years old (Blair et al. 2020). In patients who are above the age of 70 or those with markedly elevated peri-operative morbidity, prophylactic gastrectomy carries a significantly elevated risk and hence is not recommended. In individuals who decline surgery, annual endoscopy in a center with an endoscopist well-versed in HDGC is recommended (Blair et al. 2020). *Helicobacter pylori* should be eradicated if found (Blair et al. 2020). If suspicious lesions are found, especially in areas of pale mucosa or areas with rigid wall motility on inflation and suction, they should be biopsied (Treese et al. 2022). Five random biopsies from six zones of the stomach in accordance with the Cambridge biopsy protocol should be performed (Fitzgerald et al. 2010). Lifelong follow-up post prophylactic total gastrectomy should be undertaken (Blair et al. 2020). Yearly screening for lobular breast cancer or bilateral mastectomy is recommended to reduce the risk of lobular breast cancer (Blair et al. 2020).

The diagnosis of HDGC from endoscopic or surgical biopsy should be made by an experienced pathologist and reported in accordance with the World Health Organization (WHO) criteria (Smyth et al. 2016). Once the diagnosis is confirmed, staging and risk assessment should be performed which includes a contrast-enhanced computed tomography scan of the thorax, and abdomen ± pelvis. Patients should be managed in a multidisciplinary team. Total gastrectomy should be performed with intra-operative confirmation of esophageal squamous mucosa in the proximal margin and duodenal mucosa in the distal margin with D2 lymph node dissection (Blair et al. 2020). All patients should receive lifelong follow-up and special attention should be given to long-term complications of total gastrectomy symptoms, which include nutritional, hormonal, neurocognitive, psychological, and pharmacokinetic effects (van der Post et al. 2015).

Summary

Diffuse gastric cancer encompasses approximately 30% of gastric cancer diagnoses and carries a high mortality due to its late presentation and chemoresistance. Endoscopists must be familiar with its pathophysiology and diffuse presentation, which may result in it not being visualized endoscopically. Given its propensity for peritoneal disease, if the clinical suspicion remains high, there is a role for diagnostic laparoscopy. The most commonly encountered mutation in diffuse gastric cancer is *CDH1* which is part of the hereditary syndrome. The clinician should be familiar with the IGCLC diagnostic criteria of HDGC and offer genetic testing for *CDH1* and *CTNNA1* where the criteria are met. Consideration of prophylactic total gastrectomy or yearly surveillance endoscopy in those who decline surgery with biopsies performed according to the Cambridge protocol should be performed. Lifelong follow-up is needed post-total gastrectomy to monitor for its complications. Screening for lobular breast cancer with yearly imaging or prophylactic bilateral mastectomy is also recommended to reduce the risk of breast cancer.

Key Take Home Messages

1. Forms of diffuse gastric cancer can be tested by CD1 and CTNNA1 assays.
2. Lifelong screening for gastric and breast cancer is often required.

Areas for Further Research

1. Forms of cancer prevention without invasive surgery
2. Better understanding of the penetrance of the disease

Trusted Websites for Further Research

https://rarediseases.info.nih.gov/diseases/10334/diffuse-gastric-cancer

https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-digestive-system-tumors/hereditary-diffuse-gastric-cancer

References

Benusiglio, P.R., Colas, C., Guillerm, E. et al. (2019). Clinical implications of CTNNA1 germline mutations in asymptomatic carriers. *Gastric Cancer* 22 (4): 899–903.

Berx, G., Becker, K.F., Höfler, H., and Van Roy, F. (1998). Mutations of the human E-cadherin (CDH1) gene. *Hum Mutat* 12 (4): 226–237.

Blair, V.R., McLeod, M., Carneiro, F. et al. (2020). Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 21 (8): e386–e397.

Chen, Y.-C., Fang, W.-L., Wang, R.-F. et al. (2016). Clinicopathological variation of Lauren classification in gastric cancer. *Pathol Oncol Res* 22 (1): 197–202.

Cho, S.Y., Park, J.W., Liu, Y. et al. (2017). Sporadic early-onset diffuse gastric cancers have high frequency of somatic CDH1 alterations, but low frequency of somatic RHOA mutations compared with late-onset cancers. *Gastroenterology* 153 (2): 536–549. e526.

Cosma, L.-S., Schlosser, S., Tews, H.C. et al. (2022). Hereditary diffuse gastric cancer: molecular genetics, biological mechanisms and current therapeutic approaches. *Int J Mol Sci* 23 (14): 7821.

Cuschieri, A., Weeden, S., Fielding, J. et al. (1999). Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. *Br J Cancer* 79 (9): 1522–1530.

Fitzgerald, R.C., Hardwick, R., Huntsman, D. et al. (2010). Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet* 47 (7): 436–444.

Garcia-Pelaez, J., Barbosa-Matos, R., Gullo, I. et al. (2021). Histological and mutational profile of diffuse gastric cancer: current knowledge and future challenges. *Mol Oncol* 15 (11): 2841–2867.

Goud, H.K., Mehkari, Z., Mohammed, L. et al. (2020). Significance of E-cadherin gene mutations in patients with hereditary diffuse gastric cancer syndrome: a systematic review. *Cureus* 12 (9).

Guilford, P., Hopkins, J., Harraway, J. et al. (1998). E-cadherin germline mutations in familial gastric cancer. *Nature* 392 (6674): 402–405.

Hansford, S., Kaurah, P., Li-Chang, H. et al. (2015). Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol* 1 (1): 23–32.

Hartgrink, H., Van de Velde, C., Putter, H. et al. (2004). Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial.

Henson, D.E., Dittus, C., Younes, M. et al. (2004). Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973–2000: increase in the signet ring cell type. *Arch Pathol Lab Med* 128 (7): 765–770.

Iyer, P., Moslim, M., Farma, J.M., and Denlinger, C.S. (2020). Diffuse gastric cancer: histologic, molecular, and genetic basis of disease. *Transl Gastroenterol Hepatol* 5.

Katona, B.W., Clark, D.F., and Domchek, S.M. (2020). CDH1 on multigene panel testing: look before you leap. *JNCI: J Natl Cancer Inst* 112 (4): 330–334.

Kourtidis, A., Lu, R., Pence, L.J., and Anastasiadis, P.Z. (2017). A central role for cadherin signaling in cancer. *Exp Cell Res* 358 (1): 78–85.

Kumar, S., Long, J.M., Ginsberg, G.G., and Katona, B.W. (2019). The role of endoscopy in the management of hereditary diffuse gastric cancer syndrome. *World J Gastroenterol* 25 (23): 2878.

Lauren, P. (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 64 (1): 31–49.

Liu, X. and Chu, K.-M. (2014). E-cadherin and gastric cancer: cause, consequence, and applications. *BioMed Res Int* 2014.

Lo, W., Zhu, B., Sabesan, A. et al. (2019). Associations of CDH1 germline variant location and cancer phenotype in families with hereditary diffuse gastric cancer (HDGC). *J Med Genet* 56 (6): 370–379.

Luo, W., Fedda, F., Lynch, P., and Tan, D. (2018). CDH1 gene and hereditary diffuse gastric cancer syndrome: molecular and histological alterations and implications for diagnosis and treatment. *Front Pharmacol* 9: 1421.

Maître, J.-L. and Heisenberg, C.-P. (2013). Three functions of cadherins in cell adhesion. *Curr Biol* 23 (14): R626–R633.

Majewski, I.J., Kluijt, I., Cats, A. et al. (2013). An α-E-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer. *J Pathol* 229 (4): 621–629.

Melo, S., Figueiredo, J., Fernandes, M.S. et al. (2017). Predicting the functional impact of CDH1 missense mutations in hereditary diffuse gastric cancer. *Int J Mol Sci* 18 (12): 2687.

Mihmanli, M., Ilhan, E., Idiz, U.O. et al. (2016). Recent developments and innovations in gastric cancer. *World J Gastroenterol* 22 (17): 4307.

Nemtsova, M.V., Kalinkin, A.I., Kuznetsova, E.B. et al. (2020). Clinical relevance of somatic mutations in main driver genes detected in gastric cancer patients by next-generation DNA sequencing. *Sci Rep* 10 (1): 1–11.

Oliveira, C., Sousa, S., Pinheiro, H. et al. (2009). Quantification of epigenetic and genetic 2nd hits in CDH1 during hereditary diffuse gastric cancer syndrome progression. *Gastroenterology* 136 (7): 2137–2148.

Petrelli, F., Berenato, R., Turati, L. et al. (2017). Prognostic value of diffuse versus intestinal histotype in patients with gastric cancer: a systematic review and meta-analysis. *J Gastrointest Oncol* 8 (1): 148.

Rawicz-Pruszyński, K., Mielko, J., Pudło, K. et al. (2019). Yield of staging laparoscopy in gastric cancer is influenced by Lauren histologic subtype. *J Sur Oncol* 120 (7): 1148–1153.

Rocha, J.P., Gullo, I., Wen, X. et al. (2018). Pathological features of total gastrectomy specimens from asymptomatic hereditary diffuse gastric cancer patients and implications for clinical management. *Histopathology* 73 (6): 878–886.

Sasako, M., Sano, T., Yamamoto, S. et al. (2008). D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *New Engl J Med* 359 (5): 453–462.

Smyth, E., Verheij, M., Allum, W. et al. (2016). Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27: v38–v49.

Songun, I., Putter, H., Kranenbarg, E.M.-K. et al. (2010). Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 11 (5): 439–449.

Treese, C., Siegmund, B., and Daum, S. (2022). Hereditary diffuse gastric cancer—Update based on the current consort recommendations. *Curr Oncol* 29 (4): 2454–2460.

van Der Kaaij, R.T., Koemans, W.J., van Putten, M. et al. (2020). A population-based study on intestinal and diffuse type adenocarcinoma of the oesophagus and stomach in the Netherlands between 1989 and 2015. *Eur J Cancer* 130: 23–31.

van der Post, R.S., Vogelaar, I.P., Carneiro, F. et al. (2015). Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet* 52 (6): 361–374.

Wang, R., Song, S., Harada, K. et al. (2020a). Multiplex profiling of peritoneal metastases from gastric adenocarcinoma identified novel targets and molecular subtypes that predict treatment response. *Gut* 69 (1): 18–31.

Wang, S.C., Yeu, Y., Hammer, S.T. et al. (2020b). Hispanic/Latino patients with Gastric Adenocarcinoma have distinct molecular profiles including a high rate of germline CDH1 variants gastric cancer in Hispanic/Latino patients. *Cancer Res* 80 (11): 2114–2124.

Yoshiura, K., Kanai, Y., Ochiai, A. et al. (1995). Silencing of the E-cadherin invasion-suppressor gene by CpG methylation in human carcinomas. *Proceedings of the National Academy of Sciences* 92 (16): 7416–7419.

Yu, W., Yang, L., Li, T., and Zhang, Y. (2019). Cadherin signaling in cancer: its functions and role as a therapeutic target. *Front Oncol* 9: 989.

7 Intestinal-type Gastric Cancer

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Introduction

For over 100 years, gastric cancer has remained one of the most important malignant diseases with significant geographical, ethnic, and socioeconomic differences in distribution. Currently, gastric cancer is the fifth most common cancer with over one million incident cases worldwide in 2020, accounting for 5.6% of new cancers (Sung et al. 2021). It ranked the fourth for cancer-related mortality with an estimated 769,000 deaths, accounting for 7.7% of all cancer deaths. The incidence has great regional variability, being the highest in East Asia (in particular China, Japan, and Korea) where around half of the new cases are diagnosed, followed by Latin America and Eastern Europe. With the rapid decline in the global incidence of gastric cancer, the discovery of *Helicobacter pylori (H. pylori)*, and the advancement in molecular biology, the view toward gastric cancer has been changing. This chapter focuses on the intestinal type of gastric cancer, the staging system, treatment, prognosis and follow-up.

Intestinal Gastric Cancer

Gastric cancer is a heterogeneous disease entity with different proposed types of classification according to histology (Lauren and World Health Organization [WHO]) and, more recently, molecular characteristics. The Lauren classification has been traditionally used, in which gastric cancer is classified into intestinal, diffuse and mixed types, according to glandular formation (Lauren 1965). Intestinal and diffuse types are different with regard to epidemiology, etiology, pathogenesis, and behavior. For molecular characteristics, there are two classifications according to the Cancer Genome Atlas (TCGA) research group (2014) and Asian Cancer Research Group (ACRG) (Cristescu et al. 2015).

Intestinal gastric cancer is more common in male and older age groups and is likely linked to environmental factors. A recent decline in the incidence of the intestinal type in the past few decades worldwide that parallels the overall decline in the incidence of gastric cancer has been observed. The precursor lesions and environmental factors are summarized in the following section.

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Precursor Lesions and Environmental Factors

Helicobacter Pylori and the Correa's Cascade

Studies of gastric cancer among migrants have shown that emigrants from high-incidence countries to low-incidence locations often experience a decreased risk of developing gastric carcinoma. This reduction in the risk was seen in subsequent generations and to a lesser degree in the first generation (Haenszel 1982). Such findings strongly suggest that environmental factors play an important role in the etiology of gastric cancer and that exposure to risk factors occurs early in life.

The intestinal-type gastric cancer typically arises through the Correa's cascade, progressing from chronic gastritis to chronic atrophic gastritis, intestinal metaplasia, dysplasia, and eventually to adenocarcinomas (Correa 1982; Correa á 1983; Correa 1988; Correa et al. 1975). Recently, intestinal metaplasia has been recognized as a surrogate biomarker of the genetic instability that promotes the progression of gastric stem cells to cancer stem cells. The most common etiological agent triggering the Correa's cascade is *H. pylori* infection. This association has been demonstrated in large epidemiology studies (Kikuchi et al. 1995; Parsonnet et al. 1991a, 1991b; Wong et al. 1999). The WHO's International Agency for Research on Cancer classified *H. pylori* as a Group 1 or definite carcinogen (IARC WGotEoCRtH, Cancer IAfRo, Organization WH 1994). *H. pylori* infects around 50% of the population worldwide, with significant geographical variation ranging from 19% to 88% (Hooi et al. 2017). Around 1–2% of *H. pylori* infected subjects will develop gastric cancer (Uemura et al. 2001). *H. pylori* is a Gram-negative rod bacterium that localizes beneath the mucous layer of the mucosa from stomach, metaplastic esophagus, duodenum, and even Meckel's diverticulum. The *Helicobacter* genus also includes *mustelae*, *muridarum*, and *nemestrinae*, which are urease-positive but appear to be limited to stomachs of other mammals (Blaser 1992). The ability of the bacterium to survive in the acidic environment of the stomach relies on the presence of a high molecular weight urease. This enzyme catalyzes the transformation of urea to ammonium and bicarbonate, which alkalinizes the environment and protects the bacteria from gastric acid. The organism's production of proteases, lipases, phospholipases, and cytotoxins, combined with its ability to attach to epithelial cells via adherence proteins, contributes to its pathogenicity (Fennerty 1994).

Elder pointed out that 10% of patients with chronic atrophic gastritis would eventually develop gastric cancer within a period of 15 years (Elder 1995). In atrophic gastritis, there is progressive atrophy of the glandular epithelium with loss of parietal and chief cells. The loss of the normal exocrine glands of the gastric mucosa causes hypochlorhydria and a resultant increase in gastric pH. An abnormally high pH in the stomach allows microbial colonization, some of which possess nitrate reductase, allowing nitrosation that is genotoxic. In addition, there is a loss of endocrine cells which normally secrete epidermal and transforming growth factors, which aid the stomach in regenerating damaged tissue (Elder 1995). Finally, populations with a high prevalence of atrophic gastritis also have a high prevalence of gastric cancer, and vice versa (Genta 1998).

Metaplasia is a potentially reversible change from a fully differentiated cell type to another cell type, a process in adaptation to environmental stimuli. In the stomach, intestinal-type metaplasia is the most common form. This occurs as a result of *Helicobacter pylori* infection, or bile reflux (Sobala et al. 1993), or can be induced experimentally by irradiation (Watanabe 1978). Extensive gastric intestinal metaplasia refers to intestinal metaplasia involving both the antrum and corpus or corpus alone; while limited gastric intestinal metaplasia refers to involvement of only antrum or incisura (Gawron et al. 2020). Histologically, intestinal metaplasia can be classified as complete and incomplete based on the epithelial cells types (small intestine or colon) and types I to III intestinal metaplasia according to mucin types produced by the goblet cells (sialomucins and sulfomucins) (Correa et al. 2010). Intestinal metaplasia is more frequent in countries with a higher incidence of gastric carcinoma (Correa et al. 1970), and has been shown to precede gastric carcinoma (Sasajima et al. 1979). Within the gastric cancer risk index, the presence of intestinal metaplasia was the only criterion associated with the development of intestinal type gastric cancer in Japan (Shimoyama et al. 2000). Atrophy and intestinal metaplasia occur significantly more often in the antrum of carcinoma patients. The incidence rate of progression from intestinal metaplasia to dysplasia and gastric cancer is 97.6 cases and 12.4 cases per 10,000 person–years, respectively (Gawron et al. 2020). Risk factors for progression include family history of gastric cancer, extensive intestinal metaplasia and incomplete intestinal metaplasia (Gawron et al. 2020). Two validated histologic staging systems based on the degree and extent of gastric atrophy and/or intestinal metaplasia, namely Operative Link for Gastritis Assessment (OLGA) (Rugge et al. 2007) and Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) (Capelle et al. 2010) have been proposed for stratifying risk of gastric cancer. Those with OLGA or OLGIM stages III-IV are considered to be at high risk.

Most patients diagnosed with high grade dysplasia of the gastric mucosa will either already have developed or soon develop gastric cancer. In gastrectomy specimens for gastric cancer, 20–40% of patients had associated dysplasia, and progression of dysplasia to gastric cancer has been estimated at 21%, 33%, and 57% of cases of mild, moderate, and severe dysplasia, respectively (Rugge et al. 1994). In a population-based cohort study, the risk of gastric cancer increased progressively with the presence of atrophic gastritis, intestinal metaplasia and dysplasia as compared with normal gastric mucosa by a hazard ratio (HR) of 4.5, 6.2, and 10.9, respectively (Song et al. 2015).

H. pylori is associated with adenocarcinoma of non-cardia regions of the stomach, including both intestinal and diffuse types. *H. pylori* infection has been estimated to increase the risk of gastric cancer by around three fold (Cavaleiro-Pinto et al. 2011). It is estimated that *H. pylori* infection attributes to 89% of non-cardia gastric cancer cases and 78% of all gastric cancer cases (Plummer et al. 2015). On the other hand, adenocarcinoma of the cardia (accounting for 10–15% of gastric cancer) is more related to GERD, obesity and smoking (Yusefi et al. 2018). More recent evidence suggests that cardia cancer may still arise from *H-pylori*-induced atrophic gastric mucosa if two-thirds of the tumor extends into the stomach (Malfertheiner et al. 2017). Three sources of evidence support the association of *H. pylori* infection and gastric cancer: epidemiologic studies comparing gastric cancer and *H. pylori* infection prevalence rates, cross-sectional studies evaluating *H. pylori* infection in cancer patients, and prospective studies associating *H. pylori* with gastric cancer (Eurogast Study Group 1993; Forman 1991; Nomura et al. 1991; Parsonnet et al. 1991a, 1991b; Talley et al. 1991; Parsonnet 1993). Epidemiologically, the incidences of both *H. pylori* infection and gastric cancer follow similar geographic and temporal trends (Parsonnet 1993). Cross-sectional studies investigating *H. pylori* infection in gastric cancer patients have revealed that *H. pylori* is more likely to infect populations of gastric cancer patients than normal populations, with rates of infection ranging from 50% to 100% in patients with gastric adenocarcinoma (Parsonnet et al. 1991a; Parsonnet, 1993). Paradoxically, histologic association of the bacteria with tumor can be difficult to determine because *H. pylori* has an affinity for normal gastric mucosa but not metaplastic, dysplastic, or malignant tissue (Hazell et al. 1987). Prospective studies of *H. pylori* and cancer reveal that *H. pylori* infection increases the risk of developing gastric cancer in later life, although most people infected with *H. pylori* do not develop gastric carcinoma (Forman et al. 1991; Nomura et al. 1991; Parsonnet et al. 1991a). However, a paradox in *H. pylori* infection is that divergent clinical outcomes occur: patients may develop duodenal ulcer or gastric cancer, while the majority of them develop no significant clinical symptoms. Bacterial virulence factors have failed to explain why the ulcer or the gastric cancer phenotype develops. This has highlighted the need to explore host genetic factors as determinants of clinical outcome of the infection, including gastric cancer.

It is noteworthy that although *H. pylori* is the most important cause of gastric cancer, *H. pylori* eradication only reduces gastric cancer risk by 46% from a meta-analysis of seven randomized controlled trials (RCTs), six of which were conducted in East Asian countries (Ford et al. 2020). This is related the presence of baseline pre-cancerous lesions undermining the efficacy of *H. pylori* eradication in reducing gastric cancer risk (Chen et al. 2016; Wong et al. 2004). While *H. pylori* eradication reverses chronic gastritis and atrophic gastritis, it may not regress intestinal metaplasia lesions (Pimanov et al. 2008; Rokkas et al. 2007; Watari et al. 2008), which was once considered a "point of no return" in the Correa's cascade (Wong et al. 2004). However, a recent prospective study with a follow-up duration of up to 10 years did not detect difference in the prevalence of intestinal metaplasia between *H. pylori*-eradicated and *H. pylori*-negative groups in the antrum and corpus, after the follow-up periods of ≥ 5 and ≥ 3 years, respectively (Hwang et al. 2018). The probability of intestinal metaplasia reversal decreases with increasing Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) stages (Lee et al. 2021). Another study that observed 2,258 patients for up to 15 years showed that *H. pylori* eradication reduced gastric cancer risk even in those with intestinal metaplasia and dysplasia (Li et al. 2014). Moreover, *H. pylori* eradication reduces subsequent gastric cancer risk by 51% in patients who underwent endoscopic resection for gastric neoplasia (Ford et al. 2020).

The Host: Blood Group, Genetic Polymorphisms, Germline Mutation

The role of genetic factors was first suggested by the study of blood groups and determinants of chronic gastritis (Langman 1988). Individuals of blood group A have been known for decades to show approximately 20% higher rates of gastric cancer than those of group O, B, or AB. They also show a similar increase of pernicious anemia. Some data suggest that group A may be particularly associated with the diffuse type of gastric cancer (Langman 1988). A genetic etiology has been reported for chronic atrophic gastritis (Bonney et al. 1986). The genetic segregation analysis showed Mendelian transmission of a recessive autosomal gene with penetrance dependent on age and the status of chronic atrophic gastritis in the mother. Of individuals with affected mothers 48% were affected as compared to only 7% of those who mother did not have chronic atrophic gastritis. A familial tendency to stomach cancer has long been suspected and repeatedly confirmed (Langman 1988; Palli et al. 1994; Zhao et al. 1994).

The human interleukin-1 beta (IL-1B) gene is the most important candidate gene in the host that could affect the clinical outcome of *H. pylori* infection, because it is upregulated by infection, is profoundly proinflammatory, and is the most powerful acid inhibitor known. Polymorphisms in the IL-1B gene (carriers of IL-1B-511*T) and in the IL-1 receptor antagonist gene (IL-1RN*2/*2) were found to be associated with an increased risk of gastric cancer (El-Omar et al. 2000). Figueiredo, Machado, Pharoah, Seruca, Sousa, Carvalho, Capelinha, Quint, Caldas, and van Doorn (Figueiredo et al. 2002) had further suggested I L-1B-511*T carriers (IL-1B-511*T/*T or IL-1B-511*T/*C) homozygous for the short allele of IL-1RN (IL-1RN*2/*2) in the presence of vacAs1-, vacAm1-, and cagA-positive strains of *H. pylori* had an increased gastric carcinoma risk. The presence of several cytokine polymorphisms also leads to a multiplied risk of cancer.

The IFNGR1 gene encodes chain 1 of the interferon-gamma (IFN-gamma) receptor. Sequencing of IFNGR1 revealed -56C→T, H318P, and L450P variants, which were found to be associated with high *H. pylori* antibody concentrations. The variants were more prevalent in Africans than in whites. These findings indicate that IFN-gamma signaling plays an essential role in human *H. pylori* infection, and they might in part explain the observations of high prevalences and relatively low pathogenicity of *H. pylori* in Africa (Thye et al. 2003).

Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) have also been associated with gastric cancer, but mainly in East Asians (Zintzaras 2006).

A germline mutation in the cadherin 1 (*CDH1*) gene, which encodes the cell adhesion protein E-cadherin, was identified in a New Zealand family with gastric cancer (Guilford et al. 1998) and in several UK families in 1999 (Richards et al. 1999). Thereafter, in two kindreds with familial gastric cancer and germline E-cadherin mutation, promoter CpG hypermethylation was found to be the second "genetic hit" in abrogating E-cadherin expression (Grady et al. 2000). Other triggering mechanisms for inactivation of the second allele of E-cadherin include mutation and loss of heterozygosity. These results show that *CHD1* gene is an important putative tumor suppressor gene involved in gastric carcinogenesis, which has a penetrance rate of more than 60% (Oliveira et al. 2015). It is one of the causes for hereditary diffuse-type gastric cancer accounting for 1–2% of gastric cancer (Oliveira et al. 2015).

Interplay between Environmental Factors, the Organism and the Host

Tsugane et al. have found that in a Japanese population, higher salt intake correlates with higher prevalence of *H. pylori* infection (Tsugane et al. 1994). It was postulated that gastric mucosal damage caused by high salt intake facilitated *H. pylori* infection. The resultant hypochlorhydria and bacterial overgrowth, with the subsequent conversion of nitrites to the mutagenic N-nitrosamines, were postulated to be the instigating events that led to metaplasia, dysplasia, and cancer. Gastric juice of *H. pylori*-positive individuals had a lower concentration of vitamin C than *H. pylori*-negative individuals, but the concentration returned to normal when *H. pylori* was eradicated (Schorah et al. 1991). Therefore, vitamin C could play an important role in preventing the damage caused by *H. pylori* through its antioxidant effect (Schorah et al. 1991). In addition, through their anti-nitrosation and antioxidant effects, beta-carotene and ascorbic acid are believed to halt this progression to cancer and thus act as protective factors (Parsonnet 1993). However, this dogma has been supplanted by the hypothesis that *H. pylori* infection in early life leads to the formation of chronic atrophic gastritis, and the resultant transformation to metaplasia, dysplasia, and, ultimately, malignancy. The most convincing hypothesis is that chronic inflammation, with the resultant inflammation-related mutagenesis, may lead to genetic mutations culminating in malignant transformation. In addition, the resulting cellular proliferation may increase the likelihood of mitotic error and invoke a role for genotoxicity. This model also acknowledges the role of dietary factors in gastric carcinogenesis. While dietary mutagens may increase the risk of mutation, dietary antioxidants may act as protective factors. Because some DNA damage can be self-corrected, *H.* pylori-related mutations may only rarely lead to malignant transformation. Thus, longer duration of infection, especially infection acquired during childhood and continuing until old age, increases the risk of significant DNA damage with subsequent malignant transformation (Parsonnet 1993). In addition, both *H. pylori* genotype and host genetic polymorphisms play a role in determining the clinical consequences of *H. pylori* infection and hence the risk of developing gastric cancer. It has been suggested that combined bacterial/host genotyping may provide an important tool in defining disease risk and targeting *H. pylori* eradication to high-risk individuals.

Despite the proposal of dietary, environmental factors and the identification of *H. pylori*, the rapid global decline in gastric cancer is still not fully explained. An interesting hypothesis is that the introduction of refrigeration marks a pivotal point for the decline (Coggon et al. 1989; La Vecchia et al. 1990; Park et al. 2011). Refrigerators improved the storage of food, thereby reducing salting for preserving food and preventing bacterial and fungal contamination of food. Refrigeration also enables fresh food and vegetables to be more readily available, which may be a valuable source of antioxidants important for cancer prevention.

Diet

Large epidemiology studies demonstrating the association between diet and gastric cancer were mainly based on the amount of food imported and produced rather than actual food consumption (Howson et al. 1986). This takes no account of the losses during storage, distribution, and consumption of food, nor any ethnic dietary differences. Nonetheless, the information provides important insights into environmental causes of gastric cancer. The association between N-nitroso compounds and gastric cancer has been summarized by Bartsch, O'Neill, and Schulte-Hermann (Bartsch et al. 1987). The risk of gastric cancer induced by N-nitroso compounds has been demonstrated in animal experiments (Bulay et al. 1979; Druckrey 1975; Magee 1976). An increase in gastric nitrite was observed in patients with intestinal metaplasia, dysplasia, and gastric cancer (Jones et al. 1978; Stewart 1967; Ruddell et al. 1978). The use of nitrate-based fertilizers (Fraser et al. 1980; Jones et al. 1978; Schlag et al. 1980) and consumption of pickled foods that contain nitrosated products (Haenszel et al. 1972; Sato 1959) have been shown to positively correlate with gastric cancer. Diets low in vegetables, fruits, milk, and vitamin A, and high in fried food, processed meat, and fish and alcohol have been associated with an increased risk of gastric carcinoma in several cohort studies (Graham et al. 1990). Diets low in citrus fruit show the strongest association with gastric carcinoma. The protection afforded by vegetables and fruits is most likely related to their vitamin C content, which is thought to reduce the formation of carcinogenic N-nitroso compounds inside the stomach. Cooked vegetables, however, do not show the same protective effect as uncooked vegetables (Buiatti et al. 1989). High salt intake has been shown to damage stomach mucosa and increase the susceptibility to carcinogenesis in rodents (Hanawa et al. 1980; Takahashi et al. 1984; Tatematsu et al. 1975). The positive correlation between nitrate intake, salt excretion and gastric cancer has recently been shown in the INTERSALT study involving 24 countries from 39 populations (Joossens et al. 1996). A meta-analysis of 42 studies showed that smoking increased gastric cancer risk by approximately 50%, irrespective of cancer subsite (Ladeiras-Lopes et al. 2008). The risk declined significantly after 10 years of smoking cessation from a large prospective European cohort (González et al. 2003). On the other hand, an association between alcohol consumption and gastric cancer risk has not been consistently demonstrated (Barstad et al. 2005; Tramacere et al. 2012; Wang et al. 2018).

Socioeconomic Status

Risk of gastric cancer is associated with socioeconomic status. Subjects from lower socioeconomic classes had approximately twice as high a risk of developing intestinal-type gastric cancer as subjects from higher socioeconomic groups (Barker et al. 1990; Berndt et al. 1968; Haenszel 1958; Wynder et al. 1963). On the contrary, proximal gastric cancers were associated with higher socioeconomic class (Powell and McConkey 1990).

Gastric Surgery

There is an increased risk of gastric cancer after gastric surgery, with the risk being greatest 15–20 years after surgery and then increasing with time (Neugut et al. 1996; Nomura 1996). The Bilroth II procedure (gastrojejunostomy) carries a higher risk than the Bilroth I (gastroduodenostomy). It is thought this is due to the greater regurgitation of bile and pancreatic juice in the former procedure, leading to postoperative gastritis. Although still controversial, in the majority of cases gastric ulcers are not related to the eventual formation of gastric cancer.

Epstein-Barr Virus

The Epstein-Barr virus (EBV) is associated with a number of malignancies, especially nasopharyngeal carcinoma. It has been suggested that it might play a role in the development of gastric cancer also. In a study conducted in Korea (Shin et al. 1996), evidence of EBV was found in the tumor cells of 12 of 89 (13.5%) gastric carcinoma patients, whereas EBV was found in none of the gastric tissues of 37 controls with benign ulcer disease, nor in any of the benign tissues of the cases. Some of the tumor cells had a histologic appearance similar to nasopharyngeal carcinoma. In addition, EBV-associated lymphoepithelioma-like carcinoma constitutes approximately 5% of gastric cancer cases (Naseem et al. 2018).

Diabetes Mellitus

A meta-analysis of 17 observational studies showed that diabetes mellitus (DM) is associated with a 19% higher gastric cancer risk (Yoon et al. 2013). This risk persisted even after *H. pylori* eradication particularly in those with HbA1c ≥6.0% and with a more pronounced effect on cardia cancer (Cheung et al. 2019). Possible mechanisms include stimulation of cell proliferation via increased production of insulin and insulin-growth factor (IGF), promotion of angiogenesis by increasing vascular endothelial growth factor (VEGF), DNA damage by hyperglycemia and its indirect effect through an increased production of reactive oxygen species as well as its association with obesity and gastroesophageal reflux disease (GERD) (Cheung et al. 2021).

Pharmacological Agents in the Modification of Gastric Cancer Risk

Emerging evidence has shown that certain medications may modulate gastric cancer risk, including proton pump inhibitors (PPIs), aspirin, statins, and metformin. PPIs can worsen atrophic gastritis via profound acid suppression, (Kuipers et al. 1996) particularly in *H. pylori*-infected subjects (Cheung and Leung 2019; Lundell et al. 2015). The resultant increase in gastrin, which has trophic effect on the gastric mucosa, stimulates enterochromaffin-like cell hyperplasia (Lundell et al. 2015). Acid suppression also leads to non-*H. pylori* bacterial overgrowth in the stomach, which act synergistically on inducing proinflammatory cytokines (interleukin [IL]−1 beta and IL-8) and hence atrophic gastritis (Cheung and Leung 2019). There is also proliferation of non-gastric micro-organisms (mostly oral flora) that produce gastric carcinogens (N-nitroso compounds) from food nitrates via nitrate reductase (Jakszyn et al. 2006). It has been shown that PPIs are associated with a 2.5-fold higher gastric cancer risk (Salvo et al. 2021), and the risk persists even after *H. pylori* eradication (Cheung et al. 2018). However, the causality remains controversial as this is mainly based on observational studies.

Aspirin and statins are inexpensive medications for treating and preventing cardiovascular diseases. Meta-analyses reported 36% and 32% lower risks of gastric with use of aspirin (Bosetti et al. 2020) and statins (Singh and Singh 2013) respectively, and the chemopreventive effects remain even after *H. pylori* eradication (Cheung et al. 2018; Cheung et al. 2020). As for COX-2 inhibitors, one study revealed that use of rofecoxib for two years did not regress intestinal metaplasia or its severity in *H. pylori*-eradicated subjects (Leung et al. 2006), while another study showed that use of celecoxib for two years was only able to regress advanced gastric lesions in *H. pylori*-infected but not those with *H. pylori* eradication (Wong et al. 2012). Regular nonsteroidal anti-inflammatory drug (NSAID) use was associated with a 20% lower gastric cancer in a nationwide cohort study (Wu et al. 2010). Among patients with DM, metformin was associated with a 24% lower risk of gastric cancer, (Zhou et al. 2017) with protective effect even after *H. pylori* eradication (Cheung et al. 2019).

Imaging and Staging

Imaging

Computed tomography (CT) of the chest, abdomen and pelvis have been recommended as the minimal required preoperative tests for gastric cancer by the National Comprehensive Cancer Network (NCCN) (National Comprehensive Cancer Network (NCCN)). Endoscopic ultrasonography (EUS) is needed if no metastatic disease is seen on CT. The major limitations of CT as a staging study are in the evaluation of small lesions, including early gastric tumors and peritoneal or liver metastases smaller than 5 mm (Davies et al. 1997; Kim et al. 2009). Another limitation is its inability to assess the depth of tumor invasion accurately (accuracy ranging from 50–70% (Davies et al. 1997; Minami et al. 1992), typically for more advanced diseases) and the presence of lymph node metastasis particularly for nodes < 0.8 cm (Davies et al. 1997; Düx et al. 1999). Nevertheless, both over staging due to incorrect estimation of depth of invasion or false positivity of lymph node involvement attributed to inflammatory lymphadenopathy may occur. EUS has been regarded the most reliable nonsurgical modality to evaluate the depth of gastric invasion; this is particularly relevant when considering endoscopic resection. The sensitivity and specificity for distinguishing between T1 and T2 cancers with EUS were 85% and 90%, respectively, while the sensitivity and specificity for distinguishing between T1/2 and T3/4 tumors were 86% and 90%, respectively (Mocellin and Pasquali 2015). For assessment of lymph node metastasis, the sensitivity and specificity rate were 83% and 67%, respectively. EUS is better than CT at assessing the T stage and N stage (Botet et al. 1991), in particular when fine-needle aspiration (FNA) is also performed (Chang et al. 1994). Nonetheless, newer CT techniques (such as multidetector row CT [MDCT]) and magnetic resonance imaging (MRI) may have similar diagnostic performance in terms of T staging (Kwee and Kwee 2007). The combination of 18-fluorodeoxyglucose (FDG)-PET/CT imaging also improves the accuracy of preoperative staging compared with PDG-PET or CT alone (68% vs 47% vs 53% respectively) (Rosenbaum et al. 2006).

Laparoscopy is also recommended prior to chemoradiation and/or surgery. The use of laparoscopy may be supported by the fact that an R0 resection cannot be performed on 30–40% of patients undergoing surgery. Distant metastasis has been detected in patients in whom CT did not reveal signs of unresectability (Lowy et al. 1996; O'Brien et al. 1995). Intraperitoneal disease (including positive peritoneal washings) is found in 20–30% of CT-negative cases upon staging laparoscopy (Feussner et al. 1999; Lowy et al. 1996). Laparoscopy identifies CT-occult metastatic disease in 23–37% of patients (Burke et al. 1997; D'Ugo et al. 1997; Charukhchyan and Lucas 1998; Feussner et al. 1999; Possik et al. 1986; Stell et al. 1996). Moreover, fewer than 2% of the patients in these reports required subsequent laparotomy for palliation. Limitations of laparoscopy in the staging of gastric cancer include the following: (i) the technique allows for only two dimensional inspection of the surface of the liver and peritoneal cavity, (ii) it does not allow palpation, limiting the identification of small intraparenchymal hepatic metastases and perigastric lymph nodes; and (iii) laparoscopic inspection of the peritoneal surfaces does not allow critical tumor-vessel relationships to be accurately evaluated. Laparoscopic ultrasonography has been proposed as a means of overcoming some of these limitations and improving the diagnostic yield (Conlon and Karpeh 1996).

Staging

The two main staging systems for gastric cancer are the TNM staging system developed jointly by American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC), and the Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association (JGCA). The two systems are similar in that staging is dependent on the extent of the primary tumor, the extent of lymph node involvement, and the presence or absence of distant metastasis. But the difference between the two systems lies in the classification of regional lymph node spread. The AJCC/UICC TNM staging system divides N stage on the basis of the number of metastatic lymph nodes, while the Japanese classification stresses the location of involved nodes. The current main classification systems for gastric cancer are the 8th edition of the AJCC/UICC TNM classification (2017) (Table 1) (Amin et al. 2017), and the third English edition of the Japanese classification of gastric carcinoma (Japanese classification of gastric carcinoma 2011). It is important to note that gastroesophageal junction tumors with their epicenter located > 2 cm into the proximal stomach are now staged as stomach cancers in the AJCC/UICC staging.

Based on TNM staging criteria, the depth of invasion (T), presence of lymph node metastases, and number of lymph nodes involved (N) predict the risk of relapse. The AJCC/UICC TNM staging classification includes different prognostic stage entities for clinical (cTNM; patients newly diagnosed with cancer without treatment) and pathologic (pTNM; patients undergoing resection without preoperative treatment) staging including post-neoadjuvant therapy (ypTNM; patients receiving preoperative treatment) (Table 2). It is noteworthy to mention that the cTNM and ypTNM staging are newly introduced. The clinical staging was based on the National Cancer Database (NCDB) involving patients treated either surgically or nonsurgically in the United States, and Shizuoka Cancer Center dataset involving patients undergoing surgery in Japan (n=4,091). The performance was externally validated in a cohort of 4,374 surgically treated patients in Japan (Bando et al. 2019). The pathologic staging was based on International Gastric Cancer Association (IGCA) database involving >25,000 gastric cancer patients who had surgery with adequate lymph node dissection from both Asia and the West (84.8% came from Japan and Korea) (Sano et al. 2017). This was validated in a large study based on the National Cancer Database in the United States (In et al. 2017) and cohort with a higher proportion of advanced disease in Taiwan (Huang et al. 2018). For the TNM yp staging, it was based on 700 patients only and therefore only four broad staging categories (stage I–IV) are presented. By contrast, the JGCA classification is much more than a staging system. It provides comprehensive and meticulous guidance to surgeons because it describes in detail the anatomical involvement of lymph nodes.

Table 1 TNM classification of carcinoma of the stomach. (Adapted from Palis et.al., 2017).

Category	Criteria
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosa without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1–2 lymph nodes
N2	Metastases in 3–6 lymph nodes
N3	Metastases in ≥ 7 lymph nodes
N3	Metastases in 7–15 lymph nodes
N3	Metastases in ≥ 16 lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Treatment

Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD)

Therapeutic endoscopy in gastric cancer offers minimally invasive procedures that aim at complete cancer removal in early gastric cancer (EGC), which is defined as a tumor confined to the mucosa (T1a) or submucosa (T1b), irrespective of lymph node metastasis. More EGC is detected in the East than the West as a result of population-based screening programs (Chan et al. 2019). Patients with Tis or T1a tumors may be considered for EMR or endoscopic submucosal dissection (ESD) in experienced centers (National Comprehensive Cancer Network (NCCN)). For differentiated-type T1 mucosal cancers, endoscopic resection is often successful, as metastasis does not generally occur (Gotoda et al. 2000). However, it should be highlighted that lymph node metastasis may still occur in a small proportion of patients with EGC (Gotoda 2006).

General criteria of eligibility for endoscopic resection are size ≤ 2 cm without ulceration, moderately to well differentiated adenocarcinoma, confinement to mucosa and absence of lymphovascular invasion or lymph node involvement (Japanese gastric cancer treatment guidelines 2014, 2017; Ono et al. 2016; Smyth et al. 2016). Expansion of criteria have been proposed for some experienced centers (Japanese gastric cancer treatment guidelines 2014, 2017; Lee et al. 2018). The 5- and 10-year survival rates after EMR for early gastric cancer were 84% and 64% in one study (Uedo et al. 2006). ESD allows en bloc resection of larger tumors that can be treated with EMR, resulting in complete resection and lower local recurrence of early gastric cancer (Facciorusso et al. 2014; Zhao and Wang 2018). The three-year recurrence-free rate was higher in the ESD versus EMR group (98% vs 93% respectively) in a multicenter study (Oda et al. 2006). Complications of EMR and ESD include pain, bleeding, perforation, and stricture formation. Bleeding is the most common complication and is typically minor and treatable with endoscopy. The perforation rate is higher for ESD when compared with EMR, while

Table 2 Clinical, pathological and post-neoadjuvant therapy staging of carcinoma of the stomach. (Adapted from Palis et.al., 2017).

TNM staging classification			
Clinical staging (cTNM)			
	cT	**cN**	**M**
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T1	N1, N2,, or N3	M0
	T2	N1, N2 or N3	M0
Stage IIB	T3	N0	M0
	T4a	N0	M0
Stage III	T3	N1, N2, or N3	M0
	T4a	N1, N2, or N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1
Pathological staging (pTNM)			
	pT	**pN**	**M**
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1 or N2	M0
	T4b	N0	M0
Stage IIIB	T1	N3b	M0
	T2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1 or N2	M0
Stage IIIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a or N3b	M0
Stage IV	Any T	Any N	M1
Post-neoadjuvant therapy staging (ypTNM)			
	ypT	**ypN**	**M**
Stage I	T1	N0	M0
	T2	N0	M0
	T1	N1	M0
Stage II	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage III	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

bleeding risk is not significantly different (Facciorusso et al. 2014; Zhao and Wang 2018).

Laparoscopic Gastrectomy

Laparoscopic gastrectomy is intermediate between EMR and conventional surgery in terms of invasiveness. With the advances in instruments and techniques, lymph node dissection becomes possible laparoscopically and thus enables curative resection even when there is lymph node involvement. Compared with conventional open surgery, laparoscopic gastrectomy is reported to have several benefits for patients, including less blood loss, less pain, less inflammatory response, faster recovery including gastrointestinal function, preserved postoperative immune function, shorter hospital stay, reduced medical costs, and better QOL, while there is no difference in operative time, number of lymph nodes harvested, postoperative mortality and five-year overall survival (Adachi et al. 1999; Adachi et al. 2000; Adachi et al. 2002; Asao et al. 2001; Fujii et al., 2003; Migoh et al. 2003; Mochiki et al. 2002; Shimizu et al. 2000; Weber et al. 2003; Wei et al. 2018). Favorable results have been reported from several RCTs of relatively large sample size (ranging from 921 to 1416) being conducted in Asia including China, Japan and Korea (Katai et al. 2020; Kim et al. 2019; Yu et al. 2019). One RCT of much smaller sample size have been conducted in the West (Facciorusso et al. 2014), and another one is still ongoing (Straatman et al. 2015).

Robotic Surgery

Robotic gastric surgery has emerged to be an alternative minimally invasive surgical technique, although it is still not widely established. It has the merits of three-dimensional high-definition visualization, fine articulated movements and enhanced ergonomics. Compared with laparoscopic surgery, except for a longer operative time, robotic surgery has been reported to be associated with less blood loss, greater yield of lymph nodes, shorter hospital stay, similar postoperative morbidity and mortality (Hu et al. 2016).

Surgery with Intent to Cure: R0 Resection

R0 resection refers to surgery with intent to cure, while R1 resection refers to surgery with microscopic positive resection margin in the absence of distant metastasis (Hermanek and Wittekind 1994). Partial and total gastrectomy have been compared in two multicenter RCTs, (Bozzetti et al. 1999; Gouzi et al. 1989) showing no significant difference in surgical outcome but significantly fewer complications for partial gastrectomy. Therefore, partial gastrectomy is adequate for patients with gastric cancer located in the distal half of the stomach, allowing a proximal resection margin of 6 cm. The margin has to be verified by frozen section. However, a number of controversies exist over other aspects of surgical management of gastric cancer. First, the debate continues for proximal gastric cancer. Compared with total gastrectomy, proximal gastrectomy is found to improve nutrition status without compromising short-term surgical and oncologic outcomes (Tanioka et al. 2020), although larger-size studies with longer follow-up are still warranted.

The second and more important controversy is the extent of lymph node dissection. A D1 resection entails a gastrectomy with the removal of all perigastric nodes and the removal of the greater and lesser omenta. In addition to these structures, for a D2 dissection, the surgeon removes the omental bursa portion of the transverse mesocolon and the nodes along the left gastric, common hepatic, celiac, and splenic arteries. D2 dissection is technically more demanding than D1 dissection, requiring a significant experience and a steep learning curve.

The surgical strategy of the Japanese Research Society for Gastric Cancer (JRSGC) is based on the gastric lymphatic drainage. D2 radical gastrectomy has been advocated and has been practiced as standard surgery in Japan. All the lymph nodes are retrieved from the resection specimen and examined for micro-metastasis, which may sometimes be difficult to see intraoperatively. Japanese series demonstrated a survival benefit using D2 resection (Maruyama et al. 1987). It is now the standard treatment for curable gastric cancer in East Asia.

This is in contrast to the West where D1 radical gastrectomy is more commonly performed due to the lower postoperative morbidity and mortality rate and no significant difference in overall survival (Cuschieri et al. 1999; Hartgrink et al. 2004). Further, the difference could also be accounted for partially by understaging in the West where fewer regional lymph nodes were resected (Bunt et al. 1995). In addition, the Japanese tumors could have been overstaged as some of the stage I carcinomas were reported to be dysplasia by pathologists in the West (Schlemper et al. 1997). However, longer follow-up study showed that D2 resection had a lower local and regional recurrence and gastric cancer-related deaths, although overall survival difference remained statistically insignificant in. Dutch study (Songun et al. 2010). It was later found that high-volume centers with experience in operation and postoperative management had lower postoperative complications and a trend toward improved survival (Degiuli et al. 2010; Degiuli et al. 2014; Enzinger et al. 2007; Mogal et al. 2019). Currently, D2 radical gastrectomy is thus considered a recommended but not required procedure in the West, and should only be performed in experienced, high-volume centers in both NCCN and ESMO guidelines (National Comprehensive Cancer Network (NCCN); Smyth et al. 2016).

Palliative Treatment

The goal of palliative care is the achievement of the best quality of life for patients and their families (Cancer pain relief and palliative care 1990). R2 resection refers to macroscopic residual disease and is therefore considered as non-curative gastrectomy (Hermanek and Wittekind 1994). Total gastrectomy was not suggested to be worthwhile as a palliative surgery in the old days for patients with incurable disease because of the perioperative morbidity (Lawrence and McNeer 1958; ReMine 1979). However, the current view is that total palliative gastrectomy without lymph node dissection is justified in selected patients due to better symptom relief and low postoperative mortality rate, for example, perforation, uncontrollable bleeding, or gastric outlet obstruction (Izuishi and Mori 2016). Palliative gastrectomy has not been shown to prolong survival in high-quality studies. Gastrojejunostomy is preferred to endoluminal stenting in tumor obstruction, due to lower rates of symptom recurrence (Upchurch et al. 2018). Therapy for palliation can also be achieved endoscopically by recanalization or hemostasis of cancer bleeding. Endoscopic laser ablation technique is very effective in treating deeper invasive cancers.

Radiotherapy

There is little role for radiotherapy alone in the treatment of unresectable cancer (Hazard et al. 2006). Early studies showed that concurrent use with chemotherapy improved survival compared with radiotherapy alone (Hazard et al. 2006). The addition of radiotherapy to surgery has been shown to improve survival in resectable gastric cancer (Valentini et al. 2009).

Chemotherapy

The beneficial effect of perioperative chemotherapy was first shown in the MAGIC trial (Allum et al. 2003), which randomly allocated 503 cases of potentially resectable gastric cancer to either three cycles of pre- and three cycles of postoperative ECF (epirubicin, cisplatin, and 5-fluorouracil) chemotherapy, or surgery alone. The curative resection rate was increased by neoadjuvant therapy because of a significant downstaging of tumor stage (surgery only, T3 = 64%; neoadjuvant therapy T3 = 49%; p = 0.011). Perioperative chemotherapy resulted in a significant progression-free survival (PFS) and overall survival (OS). Subsequently, the FLOT4 trial, which randomly allocated patients to receive four cycles of pre- and four cycles of postoperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) or the MAGIC regimen, showed a higher proportion of patients achieving pathological complete regression with FLOT (16% vs 6%) (Al-Batran et al. 2016) and an OS benefit for FLOT group over ECG group (50 months vs 35 months) (Al-Batran et al. 2019). However, due to the toxicity associated with the FLOT regimen (serious chemotherapy-related adverse events were 27%), it is recommended that fluorouracil and oxaliplatin (FOLFOX) be used in the majority of patients with good to moderate performance status (National Comprehensive Cancer Network (NCCN)). FLOT regimen should be reserved for selected patients with good performance status. Adding radiotherapy to postoperative chemotherapy does not provide additional survival benefit if preoperative chemotherapy has been adequately given as shown in the CRITICS trial (Cats et al. 2018).

In patients who have not received preoperative chemotherapy, postoperative adjuvant chemoradiation therapy (5-fluorouracil/leucovorin and radiotherapy) has been proven to be beneficial, in particular for those with less than a D2 lymph node dissection from the INT-0116 trial conducted in the US (Dikken et al. 2010). The beneficial effect on survival remained after a median follow-up of > 10 years (Smalley et al. 2012). As for those with D2 lymph node dissection, postoperative chemotherapy with combination of capecitabine and oxaliplatin or FOLFOX is recommended based on the results of CLASSIC trial, a multi-center study conducted in South Korea, Taiwan, and China (National Comprehensive Cancer Network (NCCN); Noh et al. 2014). However, the Korean ARTIST trial did not reveal an overall survival benefit for adjuvant chemoradiation (Park et al. 2015), except for subgroup analysis showing benefit on disease-free survival in node-positive disease (Kim et al. 2016).

Hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to be potentially beneficial in selected cases after surgery for the treatment of advanced stage gastric cancer with and without peritoneal carcinomatosis (Desiderio et al. 2017). In patients without peritoneal carcinomatosis, HIPEC results in a better overall survival at three or five years when compared with control group. For those with peritoneal carcinomatosis, there is a prolonged median survival of four months despite no difference in the three-year overall survival (Desiderio et al. 2017).

It has been shown that, in RCTs, systemic chemotherapy provides palliation of symptoms, improves survival and quality of life compared to the best supportive treatment in advanced disease (Ford et al. 2014; Glimelius et al. 1997; Kang et al. 2012). Two cytotoxic drugs are preferred to three-drug cytotoxic regimen due to lower toxicity. The preferred regimens include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin (National Comprehensive Cancer Network (NCCN)). FOLFOX achieves similar efficacy compared with fluorouracil plus cisplatin but has a lower toxicity (Al-Batran et al. 2008). Irinotecan and fluorouracil (FOLFIRI) is an alternative (Guimbaud et al. 2014).

Targeted Therapy

Currently, there are three FDA-approved targeted therapies for advanced gastric cancer – trastuzumab, ramucirumab, and pembrolizumab.

Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), was first shown in the ToGA trial to prolong survival in patients with HER2-positive, locally advanced, current or metastatic, gastric or esophagogastric junction adenocarcinoma when being combined with chemotherapy (Bang et al. 2010). Its usefulness in combination with other chemotherapy regimen was further confirmed in subsequent studies (Rivera et al. 2019, Soularue et al. 2015).

Ramucirumab, a vascular endothelial growth factor receptor-2 (VEGF-2) antibody, has been shown to improve overall survival when being used as monotherapy (Fuchs et al. 2014) or in combination with chemotherapy (Wilke et al. 2014) in patients with advanced disease progressing on first-line chemotherapy. One of the sides effects is hypertension. However, it is not useful in prolonging overall survival when being added to chemotherapy in the first-line setting (Fuchs et al. 2019).

Pembrolizumab, which is a programmed cell death receptor (PD)−1 antibody, has also demonstrated promising antitumor activity against unresectable locally advanced or metastatic disease that are microsatellite instability-high (MSI-H)/defective DNA mismatch repair (dMMR) as a single agent or in combination with chemotherapy as first-line or rescue therapy (Muro et al. 2016; Shitara et al. 2020). MSI is due to the presence of dMMR system in cancers containing thousands of mutations most commonly found in monomorphic microsatellites (Luchini et al. 2019).

Therefore, it is recommended that HER2, microsatellite instability by polymerase chain reaction or mismatch repair deficiency by immunohistochemistry, and PD-L1 testing be done in patients with unresectable locally advanced or metastatic disease (National Comprehensive Cancer Network (NCCN)).

Prognosis and Follow-up

Prognosis

The prognosis of gastric cancer in the West is poorer compared with that in the East (Chan et al. 2019). There are several reasons for this difference. First, population-based screening programs results in detection of more early stage cancers in the East (e.g. Japan, Korea and the Matsu Island) whereas there are no widespread screening programs in the West (Chan et al. 2019). A recent meta-analysis showed that endoscopic screening is associated with a 40% lower risk of gastric cancer mortality (Zhang et al. 2018). Second, proximal cancer, which is more prevalent in the West, is associated with more advanced stage at presentation, larger size and poorly differentiated histology (Blot et al 1991; Chan et al. 2019; Crew and Neugut 2006). Third, D2 dissection is the standard of care in the East compared with the West. The difference in surgical techniques between the West and the East has been proposed to be a major reason for discrepancy in survival after gastrectomy – a 4.8-fold higher five-year survival probability and 67% lower risk of cancer recurrence even after adjusting for age, sex, chemotherapy, tumor depth, nodal status, and gastrectomy type (Markar et al. 2013).

The survival rates in gastric cancer have been shown to be improving in both Asian and Western countries (Arnold et al. 2019; Chen et al. 2020; Zhang et al. 2011). In a recent population-based study from 21 cancer registries covering 21 jurisdictions in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and United Kingdom), the age-standardized five-year survival has improved from 14.0–25.7% to 20.8–32.8% (absolute change ranging from 3.2 to 11.1% between the period of 1995–99 and 2010–2014 (Arnold et al. 2019). This is attributed to technological advancement enabling earlier diagnosis, better staging and better and tailored treatment (e.g. precision medicine for targeted therapies based on molecular markers). This survival improvement is more pronounced for patients younger than 75 years than those aged 75 years and older, likely to be related to the wider access to adjuvant chemotherapy and tolerance to aggressive treatments.

Nonetheless, overall prognosis of gastric cancer remains poor despite advancement in the multimodality management approach. More than half of patients presented with inoperable, advanced-stage disease (Chan et al. 2019). The recurrence rate could reach 60% even after surgery with curative intent (Liu et al. 2016). The number of lymph nodes harvested in one of the most important determining factor, and D2 dissection can reduce recurrence in this study. Currently, harvesting at least 16 lymph nodes in either D1 or a modified D2 lymph node dissection is recommended to stage the nodal status more accurately (National Comprehensive Cancer Network (NCCN)). There is a trend for improved overall survival with increasing number of lymph nodes removed for examination (Smith et al. 2005). Notably, in a study from Japan, the recurrence rate after laparoscopic gastrectomy was only around 5% (Nakagawa et al. 2014), with peritoneal metastasis being the most common (32%), followed by hematogenous spread (25%). Recurrence mostly occurs within the initial two to three years after surgery (Liu et al. 2016; Nakagawa et al. 2014).

The pathological stage has consistently been shown to be of prognostic significance for both five-year survival and local recurrence rates (Adachi et al. 2000; Roder et al. 1998; Siewert et al. 1998; Yokota et al. 2000). Siewert et al. has shown that lymph node ratio and lymph node status are the most important prognostic factors in patients with resected gastric cancer in a prospective multicenter observation trial. The data confirmed the therapeutic value of D_2 lymphadenectomy in patients with stage II disease. He also reported that in experienced centers, extended lymph node dissection does not increase the mortality or morbidity rate of resection for gastric cancer but markedly improves long-term survival in patients with stage II tumors. This effect appears to be independent of the phenomenon of stage migration. Among those with gastric resection for advanced gastric cancer, dissection of ≥ 15 lymph nodes is associated with an improved survival (Biondi et al. 2015; Schwarz and Smith 2007). In a large study based on the National Cancer Database in the United States (In et al. 2017), the five-year survival rate based on pTNM staging was 81%, 69%, 46–59%, 20–30%, and less than 10% for stage IA, stage IB, stages IIA-B, stages IIIA-B and stage IIIC-IV, respectively.

Size of the tumor is another important prognostic factor. The evidence comes from a prospective, randomized trial that demonstrated tumor size to be an independent prognostic factor in a multivariate analysis ($p=0.0002$) in patients with tumor-free margins (Siewert et al. 1998). Vascular and lymphatic permeation are both important potential independent prognostic factors. Studies have demonstrated that lymph node involvement is a statistically significant predictor of survival, and the presence of tumor emboli significantly influences tumor recurrence and death after curative resection (Yokota et al. 1999, 2000; Maehara et al. 2002). These findings were supported by other groups (Hyung et al. 2002; Kooby et al. 2003), which reported a poor prognosis associated with advanced T stage and the presence of vascular invasion (which may be a predictor of biologic aggressiveness).

Diagnostic and Prognostic Markers

The most frequently used tumor markers in gastric cancer are carcinoembryonic antigen (CEA) and CA19–9, but only a modest proportion of patients have elevated levels of these markers (Kim et al. 1995; Ohkura 1999; Pectasides et al. 1997; Yamao et al. 1999; Ychou et al. 2000). It was found in a large prospective study that preoperative positive rates for CEA and/or CA19-9 or both were 28.3% and 45.0%, respectively, among 321 patients with gastric cancer (Takahashi et al. 2003). In addition, the sensitivities of CEA and either CEA or CA19-9, or both, for recurrence were 65.8% and 85.0%, respectively, among the 120 patients who had recurrence (Takahashi et al. 2003).

Soluble E-cadherin has also been reported to have significant prognostic value (Chan et al. 2003) and to predict recurrence (Chan et al. 2005). Whether HER2 positivity has prognostic significance in general remains controversial (National

Comprehensive Cancer Network (NCCN)). However, the addition of HER2 monoclonal antibodies to chemotherapy does improve the prognosis in patients with HER2-positive metastatic disease. MMR status in tumor tissue can be identified by immunohistochemical staining to detect protein expression levels involved in DNA mismatch repair, while MSI can be assessed by polymerase chain reactions to detect gene expression levels of microsatellite makers (Luchini et al. 2019). The assessment of MSI status predicts treatment response to PD-1 blockade (i.e. pembrolizumab). The assessment of PD-L1 protein levels in tumor tissue by IHC assay using anti-PD-L1 antibodies can also help to predict response to immunotherapy (U.S. Food and Drug Administration 2017). A higher level of expression of PD-L1 and PD-1 was associated with a better survival in a German study (Böger et al. 2016). The Asian Cancer Research Group (ACRG) used gene expression profiling to define four molecular subtypes of gastric cancer with different prognosis (Cristescu et al. 2015). Epithelial to mesenchymal transition (EMT) subtype carries the worst prognosis with a high recurrence rate, while MSI subtype has the best prognosis with >50% of patients being diagnosed at an early stage and low recurrence rate (22%). The MSS subtypes have an intermediate prognosis and recurrence rate with TP53-active types showing better prognosis than TP53-inactive types.

"Liquid biopsy" in terms of evaluating circulating tumor DNA (ctDNA) in the blood to detect mutations/alterations in DNA shed from gastric cancers can help in identifying targetable alterations (e.g. MSI) and hence predicting treatment response (Willis et al. 2019). High ctDNA levels are also associated with peritoneal recurrence and worsened prognosis in advanced gastric cancer cases (Fang et al. 2016; Okabe et al. 2015).

Gastrointestinal Oncology, 2nd Edition

Intestinal Type Gastric Cancer

Key Take Home Messages

- Although gastric cancer incidence has been decreasing, it remains the fifth most common cancer and ranks the fourth for cancer-related mortality worldwide.
- Although *Helicobacter pylori* is the most important etiological factor of gastric cancer, eradication of this infection does not eliminate cancer risk in the presence of pre-existing precancerous lesions.
- Endoscopic mucosal resection and endoscopic submucosal dissection are available endoscopic therapeutic options for early gastric cancer, sparing the need of gastrectomy.
- D2 radical gastrectomy is the standard treatment for curable gastric cancer in East Asia with a survival benefit.
- D1 radical gastrectomy is more commonly performed in the West as it is technically less demanding and carries lower postoperative morbidity and mortality rate without significant difference in overall survival compared with D2 radical dissection.
- The survival rate of gastric cancer has improved due to technological advancement enabling earlier diagnosis, better staging, and tailored treatment.

Knowledge Gaps

- The traditional belief of intestinal metaplasia indicating a "point of no return" in the Correa's cascade has recently been challenged, although high-quality evidence is still lacking.
- Long-term prospective studies or even randomized clinical trials are warranted to identify potential chemopreventive agents against gastric cancer.
- Whether D2 radical gastrectomy provides a better long-term survival than D1 dissection in the West remains to be determined by further randomized clinical trials with increasing technological improvement and expertise.
- Precision medicine by integrating multi-level patient data including clinical, genetic, molecular markers will help to further predict prognosis and streamline treatment strategies.

Trusted Websites and National Evidence-based Guideline

- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

References

Adachi, Y., Shiraishi, N., and Kitano, S. (2002). Modern treatment of early gastric cancer: review of the Japanese experience. *Dig Surg* 19: 333–339.

Adachi, Y., Shiraishi, N., Shiromizu, A. et al. (2000). Laparoscopy-assisted Billroth I gastrectomy compared with conventional open gastrectomy. *Arch Surg* 135: 806–810.

Adachi, Y., Shiraishi, N., Suematsu, T. et al. (2000). Most important lymph node information in gastric cancer: multivariate prognostic study. *Ann Surg Oncol* 7: 503–507.

Adachi, Y., Suematsu, T., Shiraishi, N. et al. (1999). Quality of life after laparoscopy-assisted Billroth I gastrectomy. *Ann Surg* 229: 49.

Al-Batran, S.E., Hartmann, J.T., Probst, S. et al. (2008). Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 26: 1435–1442.

Al-Batran, S.E., Hofheinz, R.D., Pauligk, C. et al. (2016). Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol* 17: 1697–1708.

Al-Batran, S.E., Homann, N., Pauligk, C. et al. (2019). Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 393: 1948–1957.

Allum, W.H., Cunningham, D., Stenning, S.P. et al. (2003). Perioperative chemotherapy in operable gastric and lower oesophageal cancer: a randomised, controlled trial (the MAGIC trial, ISRCTN 9379 (3971) [Abstract #998]. *Proc ASCO* 22: 249a.

Amin, M.B., Edge, S.B., Greene, F.L. et al. (2017). *AJCC Cancer Staging Manual*. ed vol. 8. New York: Springer.

Arnold, M., Rutherford, M.J., Bardot, A. et al. (2019). Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol* 20: 1493–1505.

Asao, T., Hosouchi, Y., Nakabayashi, T. et al. (2001). Laparoscopically assisted total or distal gastrectomy with lymph node dissection for early gastric cancer. *J Br Surg* 88: 128–132.

Bando, E., Makuuchi, R., Irino, T. et al. (2019). Validation of the prognostic impact of the new tumor-node-metastasis clinical staging in patients with gastric cancer. *Gastric Cancer* 22: 123–129.

Bang, Y.J., Van Cutsem, E., Feyereislova, A. et al. (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 376: 687–697.

Barker, D., Coggon, D., Osmond, C. et al. (1990). Poor housing in childhood and high rates of stomach cancer in England and Wales. *Br J Cancer* 61: 575–578.

Barstad, B., Sørensen, T.I., Tjønneland, A. et al. (2005). Intake of wine, beer and spirits and risk of gastric cancer. *Eur J Cancer Prev* 14: 239–243.

Bartsch, H., O'Neill, I., and Schulte-Hermann, R. (1987). Relevance of N-nitroso compounds to human cancer: exposures and mechanisms: *Proceedings of the IXth International Symposium on N-nitroso Compounds, Held in Baden*. Austria: Oxford University Press. 1-5 September 1986.

Berndt, H., Wildner, G., and Klein, K. (1968). Regional and social differences in cancer incidence of the digestive tract in the German Democratic Republic. *Neoplasma* 15: 501–515.

Biondi, A., D'Ugo, D., Cananzi, F.C. et al. (2015). Does a minimum number of 16 retrieved nodes affect survival in curatively resected gastric cancer? *Eur J Surg Oncol* 41: 779–786.

Blaser, M.J. (1992). Helicobacter pylori: its role in disease. *Clin Inf Dis* 15: 386–391.

Blot, W.J., Devesa, S.S., Kneller, R.W. et al. (1991). Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 265: 1287–1289.

Böger, C., Behrens, H.M., Mathiak, M. et al. (2016). PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. *Oncotarget* 7: 24269–24283.

Bonney, G.E., Elston, R.C., Correa, P. et al. (1986). Genetic etiology of gastric carcinoma: i. Chronic Atrophic Gastritis. *Genet Epidemiol* 3: 213–224.

Bosetti, C., Santucci, C., Gallus, S. et al. (2020). Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol* 31: 558–568.

Botet, J.F., Lightdale, C.J., Zauber, A.G. et al. (1991). Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. *Radiology* 181: 426–432.

Bozzetti, F., Marubini, E., Bonfanti, G. et al. (1999). Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. *Ann Surg* 230: 170.

Buiatti, E., Palli, D., Decarli, A. et al. (1989). A case-control study of gastric cancer and diet in Italy. *Int J Cancer* 44: 611–616.

Bulay, O., Mlrvish, S.S., Garcia, H. et al. (1979). Carcinogenicity test of six nitrosamides and a nitrosocyanamide administered orally to rats. *J Natl Cancer Inst* 62: 1523–1528.

Bunt, A., Hermans, J., Smit, V. et al. (1995). Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 13: 19–25.

Burke, E.C., Karpeh, M., Conlon, K.C. et al. (1997). Laparoscopy in the management of gastric adenocarcinoma. *Ann Surg* 225: 262.

Cancer pain relief and palliative care. (1990). Report of a WHO Expert committee. *World Health Organ Tech Rep Ser* 804: 1–75.

Capelle, L.G., de Vries, A.C., Haringsma, J. et al. (2010). The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointest Endosc* 71: 1150–1158.

Cats, A., Jansen, E.P.M., NCT, V.G. et al. (2018). Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 19: 616–628.

Cavaleiro-Pinto, M., Peleteiro, B., Lunet, N. et al. (2011). Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control* 22: 375–387.

Chan, A.O.O., Chu, K.M., Lam, S.K. et al. (2005). Early prediction of tumor recurrence after curative resection of gastric carcinoma by measuring soluble E-cadherin. *Cancer* 104: 740–746.

Chan, A.-O.-O., Chu, K.-M., Lam, S.-K. et al. (2003). Soluble E-cadherin is an independent pretherapeutic factor for long-term survival in gastric cancer. *J Clin Oncol* 21: 2288–2293.

Chan, W.L., Lam, K.O., Lee, V.H.F. et al. (2019). Gastric cancer - From Aetiology to management: differences between the East and the West. *Clin Oncol (R Coll Radiol)* 31: 570–577.

Chang, K.J., Katz, K.D., Durbin, T.E. et al. (1994). Endoscopic ultrasound-guided fine-needle aspiration. *Gastrointest Endosc* 40: 694–699.

Charukhchyan, S.A. and Lucas, G.W. (1998). Laparoscopy and lesser sac endoscopy in gastric carcinoma operability assessment. *Am Surg* 64: 160.

Chen, H.N., Wang, Z., Li, X. et al. (2016). Helicobacter pylori eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. *Gastric Cancer* 19: 166–175.

Chen, Q., Liu, S.Z., Zhang, S.K. et al. (2020). The relative survival and cure fraction of gastric cancer estimated through flexible parametric models using data from population-based cancer registration during 2003-2012 in Linzhou, China. *Cancer Med* 9: 2243–2251.

Cheung, K.S., Chan, E.W., Chen, L. et al. (2019). Diabetes increases risk of gastric cancer after Helicobacter pylori Eradication: a territory-wide study with propensity score analysis. *Diabetes Care* 42: 1769–1775.

Cheung, K.S., Chan, E.W., Wong, A.Y.S. et al. (2018). Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. *Gut* 67: 28–35.

Cheung, K.S., Chan, E.W., Wong, A.Y.S. et al. (2018). Aspirin and risk of gastric cancer after Helicobacter pylori Eradication: a Territory-Wide study. *J Natl Cancer Inst* 110: 743–749.

Cheung, K.S., Chan, E.W., Wong, A.Y.S. et al. (2019). Metformin use and gastric cancer risk in diabetic patients after Helicobacter pylori eradication. *J Natl Cancer Inst* 111: 484–489.

Cheung, K.S., Chan, E.W., Wong, A.Y.S. et al. (2020). Statins were associated with a reduced gastric cancer risk in patients with eradicated Helicobacter Pylori infection: a territory-wide propensity score matched study. *Cancer Epidemiol Biomarkers Prev* 29: 493–499.

Cheung, K.S., Chung, K.L., and Leung, W.K. (2021). Chemopreventive effect of Metformin on gastric cancer development. *Gut Liver* 16: 147–156.

Cheung, K.S. and Leung, W.K. (2019). Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. *Therap Adv Gastroenterol* 12: 1756284819834511.

Coggon, D., Barker, D.J., Cole, R.B. et al. (1989). Stomach cancer and food storage. *JNCI: J Natl Cancer Inst* 81: 1178–1182.

Cancer Genome Atlas Research Network. (2014). Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 513: 202–209.

Conlon, K.C. and Karpeh, M.S., Jr. (1996). Laparoscopy and laparoscopic ultrasound in the staging of gastric cancer. *Semin Oncol* 23: 347–351.

Correa á (1983). The gastric precancerous process. *Cancer Surv* 2: 438–450.

Correa, P. (1982a). Precursors of gastric and esophageal cancer. *Cancer* 50: 2554–2565.

Correa, P. (1988). A human model of gastric carcinogenesis. *Cancer Res* 48: 3554–3560.

Correa, P., Cuello, C., and Duque, E. (1970). Carcinoma and intestinal metaplasia of the stomach in Colombian migrants. *J Natl Cancer Inst* 44: 297–306.

Correa, P., Haenszel, W., Cuello, C. et al. (1975). A model for gastric cancer epidemiology. *Lancet* 306: 58–60.

Correa, P., Haenszel, W., and Tannenbaum, S. (1982b). Epidemiology of gastric carcinoma: review and future prospects. *Natl Cancer Inst Monogr* 62: 129–134.

Correa, P., Piazuelo, M.B., and Wilson, K.T. (2010). Pathology of gastric intestinal metaplasia: clinical implications. *Am J Gastroenterol* 105: 493–498.

Crew, K.D. and Neugut, A.I. (2006). Epidemiology of gastric cancer. *World J Gastroenterol* 12: 354–362.

Cristescu, R., Lee, J., Nebozhyn, M. et al. (2015). Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 21: 449–456.

Cuschieri, A., Weeden, S., Fielding, J. et al. (1999). Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. surgical Co-operative Group. *Br J Cancer* 79: 1522–1530.

D'Ugo, D., Persiani, R., Caracciolo, F. et al. (1997). Selection of locally advanced gastric carcinoma by preoperative staging laparoscopy. *Surg Endosc* 11: 1159–1162.

Davies, J., Chalmers, A., Sue-Ling, H. et al. (1997). Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. *Gut* 41: 314–319.

Davies, J., Chalmers, A.G., Sue-Ling, H.M. et al. (1997). Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. *Gut* 41: 314–319.

Degiuli, M., Sasako, M., and Ponti, A. (2010). Morbidity and mortality in the Italian gastric cancer study group randomized clinical trial of D1 versus D2 resection for gastric cancer. *Br J Surg* 97: 643–649.

Degiuli, M., Sasako, M., Ponti, A. et al. (2014). Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. *Br J Surg* 101: 23–31.

Desiderio, J., Chao, J., Melstrom, L. et al. (2017). The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer* 79: 1–14.

Dikken, J.L., Jansen, E.P., Cats, A. et al. (2010). Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. *J Clin Oncol* 28: 2430–2436.

Druckrey, H. (1975). Chemical carcinogenesis on N-nitroso derivatives. *Gann Monogr* 17: 107–132.

Düx, M., Richter, G.M., Hansmann, J. et al. (1999). Helical hydro-CT for diagnosis and staging of gastric carcinoma. *J Comput Assist Tomogr* 23: 913–922.

Soularue, É., Cohen, R., Tournigand, C. et al. (2015). Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study. *Bull Cancer* 102: 324–331.

Elder, J. (1995). Carcinoma of the stomach. In: *Bockus Gastroenterology*, vol. ume I (ed. W.S.S.F. Haubrich and J.E. Berk), 5e. 805–815. Philadelphia: WB Saunders Co.

El-Omar, E.M., Carrington, M., Chow, W.-H. et al. (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 404: 398–402.

Enzinger, P.C., Benedetti, J.K., Meyerhardt, J.A. et al. (2007). Impact of hospital volume on recurrence and survival after surgery for gastric cancer. *Ann Surg* 245: 426–434.

Eurogast Study Group (1993). An international association between Helicobacter pylori infection and gastric cancer. *Lancet* 341: 1359–1363.

Facciorusso, A., Antonino, M., Di Maso, M. et al. (2014). Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: a meta-analysis. *World J Gastrointest Endosc* 6: 555–563.

Fang, W.L., Lan, Y.T., Huang, K.H. et al. (2016). Clinical significance of circulating plasma DNA in gastric cancer. *Int J Cancer* 138: 2974–2983.

Fennerty, M.B. (1994). Helicobacter pylori. *Arch Intern Med* 154: 721–727.

Feussner, H., Omote, K., Fink, U. et al. (1999). Pretherapeutic laparoscopic staging in advanced gastric carcinoma. *Endoscopy* 31: 342–347.

Figueiredo, C., Machado, J.C., Pharoah, P. et al. (2002). Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst* 94: 1680–1687.

Ford, A.C., Yuan, Y., and Moayyedi, P. (2020). Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut* 69: 2113–2121.

Ford, H.E., Marshall, A., Bridgewater, J.A. et al. (2014). Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 15: 78–86.

Forman, D. (1991). *Helicobacter Pylori Infection: A Novel Risk Factor in the Etiology of Gastric Cancer*. Oxford University Press.

Forman, D., Newell, D., Fullerton, F. et al. (1991). Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. *Br Med J* 302: 1302–1305.

Fraser, P., Chilvers, C., Beral, V. et al. (1980). Nitrata and human cancer: a review of the evidence. *Int J Epidemiol* 9: 3–12.

Fuchs, C.S., Shitara, K., Di Bartolomeo, M. et al. (2019). Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 20: 420–435.

Fuchs, C.S., Tomasek, J., Yong, C.J. et al. (2014). Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 383: 31–39.

Fujii, K., Sonoda, K., Izumi, K. et al. (2003). T lymphocyte subsets and Th1/Th2 balance after laparoscopy-assisted distal gastrectomy. *Surg Endosc Other Interv Tech* 17: 1440–1444.

Gawron, A.J., Shah, S.C., Altayar, O. et al. (2020). AGA technical review on gastric intestinal metaplasia-natural history and clinical outcomes. *Gastroenterology* 158 (705–731.e5).

Genta, R. (1998). Acid suppression and gastric atrophy: sifting fact from fiction. *Gut* 43: S35.

Glimelius, B., Ekström, K., Hoffman, K. et al. (1997). Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 8: 163–168.

González, C.A., Pera, G., Agudo, A. et al. (2003). Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer* 107: 629–634.

Gotoda, T. (2006). Endoscopic resection of early gastric cancer: the Japanese perspective. *Curr Opin Gastroenterol* 22: 561–569.

Gotoda, T., Yanagisawa, A., Sasako, M. et al. (2000). Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 3: 219–225.

Gouzi, J., Huguier, M., Fagniez, P. et al. (1989). Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 209: 162.

Grady, W.M., Willis, J., Guilford, P.J. et al. (2000). Methylation of the CDH1 promoter as the second genetic hit in hereditary diffuse gastric cancer. *Nat Genet* 26: 16–17.

Graham, S., Haughey, B., Marshall, J. et al. (1990). Diet in the epidemiology of gastric cancer.

Guilford, P., Hopkins, J., Harraway, J. et al. (1998). E-cadherin germline mutations in familial gastric cancer. *Nature* 392: 402–405.

Guimbaud, R., Louvet, C., Ries, P. et al. (2014). Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. *J Clin Oncol* 32: 3520–3526.

Haenszel, W. (1958). Variation in incidence of and mortality from stomach cancer, with particular reference to the United States. *J Natl Cancer Inst* 21: 213–262.

Haenszel, W. (1982). Migrant studies In: *Cancer Epidemiology and Prevention: WB Saunders* (ed. D.F.J. Schottenfeld), 194–207. Philadelphia: Saunders.

Haenszel, W., Kurihara, M., Segi, M. et al. (1972). Stomach cancer among Japanese in Hawaii. *J Natl Cancer Inst* 49: 969–988.

Hanawa, K., Yamada, S., and Suzuki, H. (1980). Effects of sodium chloride on gastric cancer induction by N-methyl-N-Nitro-N-nitrogoguanidine (MNNG) in rats. In: *Proceedings of the Thirty-ninth Annual Meeting of the Japanese Cancer Association*. Tokyo: Japanese Cancer Association.

Hartgrink, H.H., van de Velde, C.J., Putter, H. et al. (2004). Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 22: 2069–2077.

Hazard, L., O'Connor, J., and Scaife, C. (2006). Role of radiation therapy in gastric adenocarcinoma. *World J Gastroenterol* 12: 1511–1520.

Hazell, S., Hennessy, W., Borody, T. et al. (1987). Campylobacter pyloridis gastritis II: distribution of bacteria and associated inflammation in the gastroduodenal environment. *Am J Gastroenterol (Springer Nature)* 82.

Hermanek, P. and Wittekind, C. (1994). Residual tumor (R) classification and prognosis. *Semin Surg Oncol* 10: 12–20.

Hooi, J.K.Y., Lai, W.Y., Ng, W.K. et al. (2017). Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology* 153: 420–429.

Howson, C.P., Hiyama, T., and Wynder, E.L. (1986). The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev* 8: 1–27.

Hu, L.D., Li, X.F., Wang, X.Y. et al. (2016). Robotic versus Laparoscopic Gastrectomy for Gastric Carcinoma: a Meta-Analysis of Efficacy and Safety. *Asian Pac J Cancer Prev* 17: 4327–4333.

Huang, S.F., Chien, T.H., Fang, W.L. et al. (2018). The 8th edition American Joint Committee on gastric cancer pathological staging classification performs well in a population with high proportion of locally advanced disease. *Eur J Surg Oncol* 44: 1634–1639.

Hwang, Y.J., Kim, N., Lee, H.S. et al. (2018). Reversibility of atrophic gastritis and intestinal metaplasia after Helicobacter pylori eradication - a prospective study for up to 10 years. *Aliment Pharmacol Ther* 47: 380–390.

Hyung, W.J., Lee, J.H., Choi, S.H. et al. (2002). Prognostic impact of lymphatic and/or blood vessel invasion in patients with node-negative advanced gastric cancer. *Ann Surg Oncol* 9: 562–567.

IARC WGotEoCRtH, Cancer IAfRo, Organization WH. (1994). Schistosomes, Liver Flukes and Helicobacter Pylori: International Agency for Research on Cancer.

In, H., Solsky, I., Palis, B. et al. (2017). Validation of the 8th Edition of the AJCC TNM staging system for gastric Cancer using the National Cancer database. *Ann Surg Oncol* 24: 3683–3691.

Izuishi, K. and Mori, H. (2016). Recent strategies for treating stage IV gastric cancer: roles of palliative gastrectomy, chemotherapy, and radiotherapy. *J Gastrointestin Liver Dis* 25: 87–94.

Jakszyn, P., Bingham, S., Pera, G. et al. (2006). Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. *Carcinogenesis* 27: 1497–1501.

Japanese classification of gastric carcinoma (2011). 3rd English edition. *Gastric Cancer* 14: 101–112.

Japanese gastric cancer treatment guidelines 2014 (2017). ver. 4. *Gastric Cancer* 20: 1–19.

Jones, S., Davies, P., and Savage, A. (1978). Gastric-juice nitrite and gastric cancer. *Lancet* 311: 1355.

Joossens, J.V., Hill, M., Elliott, P. et al. (1996). Dietary salt, nitrate and stomach cancer mortality in 24 countries. *Int J Epidemiol* 25: 494–504.

Kang, J.H., Lee, S.I., Lim, D.H. et al. (2012). Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 30: 1513–1518.

Katai, H., Mizusawa, J., Katayama, H. et al. (2020). Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol* 5: 142–151.

Kikuchi, S., Wada, O., Nakajima, T. et al. (1995). Serum anti-Helicobacter pylori antibody and gastric carcinoma among young adults. *Cancer* 75: 2789–2793.

Kim, H.H., Han, S.U., Kim, M.C. et al. (2019). Effect of laparoscopic distal gastrectomy vs open distal gastrectomy on long-term survival among patients with stage I gastric cancer: the KLASS-01 randomized clinical trial. *JAMA Oncol* 5: 506–513.

Kim, S.J., Kim, H.H., Kim, Y.H. et al. (2009). Peritoneal metastasis: detection with 16- or 64-detector row CT in patients undergoing surgery for gastric cancer. *Radiology* 253: 407–415.

Kim, Y., Park, S.H., Kim, K.M. et al. (2016). The influence of metastatic lymph node ratio on the treatment outcomes in the adjuvant chemoradiotherapy in stomach tumors (ARTIST) trial: a phase III trial. *J Gastric Cancer* 16: 105–110.

Kim, Y.H., Ajani, J.A., Ota, D.M. et al. (1995). Value of serial carcinoembryonic antigen levels in patients with resectable adenocarcinoma of the esophagus and stomach. *Cancer* 75: 451–456.

Kooby, D.A., Suriawinata, A., Klimstra, D.S. et al. (2003). Biologic predictors of survival in node-negative gastric cancer. *Ann Surg* 237: 828–835. discussion 835-7.

Kuipers, E.J., Lundell, L., Klinkenberg-Knol, E.C. et al. (1996). Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 334: 1018–1022.

Kwee, R.M. and Kwee, T.C. (2007). Imaging in local staging of gastric cancer: a systematic review. *J Clin Oncol* 25: 2107–2116.

La Vecchia, C., Negri, E., d'Avanzo, B. et al. (1990). Electric refrigerator use and gastric cancer risk. *Br J Cancer* 62: 136.

Ladeiras-Lopes, R., Pereira, A.K., Nogueira, A. et al. (2008). Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control* 19: 689–701.

Langman, M. (1988). Genetic influences upon gastric cancer frequency. In: *Gastric Carcinogenesis* (ed. P.I.H.M. Reed), 81–86. Amsterdam: Excerpta Medica.

Lauren, P. (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 64: 31–49.

Lawrence, J.W. and McNeer, G. (1958). The effectiveness of surgery for palliation of incurable gastric cancer. *Cancer* 11: 28–32.

Lee, J.W.J., Zhu, F., Srivastava, S. et al. (2021). Severity of gastric intestinal metaplasia predicts the risk of gastric cancer: a prospective multicentre cohort study (GCEP) *Gut* 71: 854–863.

Lee, S., Choi, K.D., Han, M. et al. (2018). Long-term outcomes of endoscopic submucosal dissection versus surgery in early gastric cancer meeting expanded indication including undifferentiated-type tumors: a criteria-based analysis. *Gastric Cancer* 21: 490–499.

Leung, W.K., Ng, E.K., Chan, F.K. et al. (2006). Effects of long-term rofecoxib on gastric intestinal metaplasia: results of a randomized controlled trial. *Clin Cancer Res* 12: 4766–4772.

Li, W.Q., Ma, J.L., Zhang, L. et al. (2014). Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. *J Natl Cancer Inst* 106.

Liu, D., Lu, M., Li, J. et al. (2016). The patterns and timing of recurrence after curative resection for gastric cancer in China. *World J Surg Oncol* 14: 305.

Lowy, A.M., Mansfield, P.F., Leach, S.D. et al. (1996). Laparoscopic staging for gastric cancer. *Surgery* 119: 611–614.

Luchini, C., Bibeau, F., Ligtenberg, M.J.L. et al. (2019). ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Ann Oncol* 30: 1232–1243.

Lundell, L., Vieth, M., Gibson, F. et al. (2015). Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. *Aliment Pharmacol Ther* 42: 649–663.

Maehara, Y., Kakeji, Y., Koga, T. et al. (2002). Therapeutic value of lymph node dissection and the clinical outcome for patients with gastric cancer. *Surgery* 131: S85–S91.

Magee, P. (1976). N-Nitroso compounds and related carcinogens. In: *Chemical Carcinogens* (ed. S. CE), vol. 173. 491–625. ACS Monograph.

Malfertheiner, P., Megraud, F., O'Morain, C.A. et al. (2017). Management of Helicobacter pylori infection-the Maastricht V/Florence consensus report. *Gut* 66: 6–30.

Markar, S.R., Karthikesalingam, A., Jackson, D. et al. (2013). Long-term survival after gastrectomy for cancer in randomized, controlled oncological trials: comparison between West and East. *Ann Surg Oncol* 20: 2328–2338.

Maruyama, K., Okabayashi, K., and Kinoshita, T. (1987). Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 11: 418–425.

Migoh, S., Hasuda, K., Nakashima, K. et al. (2003). The benefit of laparoscopy-assisted distal gastrectomy compared with conventional open distal gastrectomy: a case-matched control study. *Hepato-gastroenterology* 50: 2251–2254.

Minami, M., Kawauchi, N., Itai, Y. et al. (1992). Gastric tumors: radiologic-pathologic correlation and accuracy of T staging with dynamic CT. *Radiology* 185: 173–178.

Mocellin, S. and Pasquali, S. (2015). Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. *Cochrane Database Syst Rev* 2015: Cd009944.

Mochiki, E., Nakabayashi, T., Kamimura, H. et al. (2002). Gastrointestinal recovery and outcome after laparoscopy-assisted versus conventional open distal gastrectomy for early gastric cancer. *World J Surg* 26: 1145–1149.

Mogal, H., Fields, R., Maithel, S.K. et al. (2019). In patients with localized and resectable gastric cancer, what is the optimal extent of lymph node dissection-D1 Versus D2 Versus D3? *Ann Surg Oncol* 26: 2912–2932.

Muro, K., Chung, H.C., Shankaran, V. et al. (2016). Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 17: 717–726.

Nakagawa, M., Kojima, K., Inokuchi, M. et al. (2014). Patterns, timing and risk factors of recurrence of gastric cancer after laparoscopic gastrectomy: reliable results following long-term follow-up. *Eur J Surg Oncol* 40: 1376–1382.

Naseem, M., Barzi, A., Brezden-Masley, C. et al. (2018). Outlooks on Epstein-Barr virus associated gastric cancer. *Cancer Treat Rev* 66: 15–22.

National Comprehensive Cancer Network (NCCN). (2022). NCCN clinical practice guidelines in oncology. https://www.nccn.org/professionals/physician_gls

Neugut, A.I., Hayek, M., and Howe, G. (1996). Epidemiology of gastric cancer. *Semin Oncol* 23: 281–91.

Noh, S.H., Park, S.R., Yang, H.K. et al. (2014). Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 15: 1389–1396.

Nomura, A. (1996). Stomach cancer. In: *Cancer Epidemiology and Prevention*, 2e (ed. D.F.J.J. Scottenfeld), NY: Oxford University Press.

Nomura, A., Stemmermann, G.N., Chyou, P.-H. et al. (1991). Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. *New Engl J Med* 325: 1132–1136.

O'Brien, M.G., Fitzgerald, E.F., Lee, G. et al. (1995). A prospective comparison of laparoscopy and imaging in the staging of esophagogastric cancer before surgery. *Am J Gastroenterol (Springer Nature)* 90.

Oda, I., Saito, D., Tada, M. et al. (2006). A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 9: 262–270.

Ohkura, H. (1999). Tumor markers in monitoring response to chemotherapy for patients with gastric cancer: Foundation for Promotion of Cancer Research.

Okabe, H., Tsunoda, S., Hosogi, H. et al. (2015). Circulating tumor cells as an independent predictor of survival in advanced gastric cancer. *Ann Surg Oncol* 22: 3954–3961.

Oliveira, C., Pinheiro, H., Figueiredo, J. et al. (2015). Familial gastric cancer: genetic susceptibility, pathology, and implications for management. *Lancet Oncol* 16: e60–70.

Ono, H., Yao, K., Fujishiro, M. et al. (2016). Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 28: 3–15.

Palli, D., Galli, M., Caporaso, N.E. et al. (1994). Family history and risk of stomach cancer in Italy. *Cancer Epidemiol Prev Biomark* 3: 15–18.

Park, B., Shin, A., Park, S.K. et al. (2011). Ecological study for refrigerator use, salt, vegetable, and fruit intakes, and gastric cancer. *Cancer Causes Control* 22: 1497–1502.

Park, S.H., Sohn, T.S., Lee, J. et al. (2015). Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 33: 3130–3136.

Parsonnet, J. (1993). Helicobacter pylori and gastric cancer. *Gastroenterol Clin North Am* 22: 89–104.

Parsonnet, J., Friedman, G.D., Vandersteen, D.P. et al. (1991a). Helicobacter pylori infection and the risk of gastric carcinoma. *New Engl J Med* 325: 1127–1131.

Parsonnet, J., Vandersteen, D., Goates, J. et al. (1991b). Helicobacter pylori infection in intestinal-and diffuse-type gastric adenocarcinomas. *JNCI: J Natl Cancer Inst* 83: 640–643.

Pectasides, D., Mylonakis, A., Kostopoulou, M. et al. (1997). CEA, CA 19-9, and CA-50 in monitoring gastric carcinoma. *Am J Clin Oncol* 20: 348–353.

Pimanov, S.I., Makarenko, E.V., Voropaeva, A.V. et al. (2008). Helicobacter pylori eradication improves gastric histology and decreases serum gastrin, pepsinogen I and pepsinogen II levels in patients with duodenal ulcer. *J Gastroenterol Hepatol* 23: 1666–1671.

Plummer, M., Franceschi, S., Vignat, J. et al. (2015). Global burden of gastric cancer attributable to Helicobacter pylori. *Int J Cancer* 136: 487–490.

Possik, R.A., Franco, E.L., Pires, D.R. et al. (1986). Sensitivity, specificity, and predictive value of laparoscopy for the staging of gastric cancer and for the detection of liver metastases. *Cancer* 58: 1–6.

Powell, J. and McConkey, C. (1990). Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 62: 440–443.

ReMine, W.H. (1979). Palliative operations for incurable gastric cancer. *World J Surg* 3: 721–726.

Richards, F.M., McKee, S.A., Rajpar, M.H. et al. (1999). Germline E-cadherin gene (CDH1) mutations predispose to familial gastric cancer and colorectal cancer. *Human Molecular Genetics* 8: 607–610.

Rivera, F., Romero, C., Jimenez-Fonseca, P. et al. (2019). Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial. *Cancer Chemother Pharmacol* 83: 1175–1181.

Roder, J.D., Böttcher, K., Busch, R. et al. (1998). Classification of regional lymph node metastasis from gastric carcinoma. *Cancer: Interdisciplinary Int J Am Cancer Soc* 82: 621–631.

Rokkas, T., Pistiolas, D., Sechopoulos, P. et al. (2007). The long-term impact of Helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. *Helicobacter* 12 (Suppl 2): 32–38.

Rosenbaum, S.J., Stergar, H., Antoch, G. et al. (2006). Staging and follow-up of gastrointestinal tumors with PET/CT. *Abdom Imaging* 31: 25–35.

Ruddell, W., Bone, E., Hill, M. et al. (1978). Pathogenesis of gastric cancer in pernicious anaemia. *Lancet* 311: 521–523.

Rugge, M., Farinati, F., Baffa, R. et al. (1994). Gastric epithelial dysplasia in the natural history of gastric cancer: a multicenter prospective follow-up study. *Gastroenterology* 107: 1288–1296.

Rugge, M., Meggio, A., Pennelli, G. et al. (2007). Gastritis staging in clinical practice: the OLGA staging system. *Gut* 56: 631–636.

Salvo, E.M., Ferko, N.C., Cash, S.B. et al. (2021). Umbrella review of 42 systematic reviews with meta-analyses: the safety of proton pump inhibitors. *Aliment Pharmacol Ther* 54: 129–143.

Sano, T., Coit, D.G., Kim, H.H. et al. (2017). Proposal of a new stage grouping of gastric cancer for TNM classification: international gastric cancer association staging project. *Gastric Cancer* 20: 217–225.

Sasajima, K., Kawachi, T., Matsukura, N. et al. (1979). Intestinal metaplasia and adenocarcinoma induced in the stomach of rats by N-propyl-N′-nitro-N-nitrosoguanidine. *J Cancer Res Clin Oncol* 94: 201–206.

Sato, T. (1959). Studies of causation of gastric cancer. 2. The relation between gastric cancer mortality rate and salted food intake in several places in Japan. *Bull Inst Public Health* 8: 187–198.

Schlag, P., Ulrich, H., Merkle, P. et al. (1980). Are nitrite and N-nitroso compounds in gastric juice risk factors for carcinoma in the operated stomach? *Lancet* 315: 727–729.

Schlemper, R.J., Itabashi, M., Kato, Y. et al. (1997). Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. *Lancet* 349: 1725–1729.

Schorah, C.J., Sobala, G.M., Sanderson, M. et al. (1991). Gastric juice ascorbic acid: effects of disease and implications for gastric carcinogenesis. *Am J Clin Nutr* 53: 287S–293S.

Schwarz, R.E. and Smith, D.D. (2007). Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. *Ann Surg Oncol* 14: 317–328.

Shimizu, S., Uchiyama, A., Mizumoto, K. et al. (2000). Laparoscopically assisted distal gastrectomy for early gastric cancer. *Surg Endosc* 14: 27–31.

Shimoyama, T., Fukuda, S., Tanaka, M. et al. (2000). Evaluation of the applicability of the gastric carcinoma risk index for intestinal type cancer in Japanese patients infected with Helicobacter pylori. *Virchows Archiv* 436: 585–587.

Shin, W.S., Kang, M.W., Kang, J.H. et al. (1996). Epstein-Barr virus-associated gastric adenocarcinomas among Koreans. *Am J Clin Pathol* 105: 174–181.

Shitara, K., Van Cutsem, E., Bang, Y.J. et al. (2020). Efficacy and safety of Pembrolizumab or Pembrolizumab plus chemotherapy vs Chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol* 6: 1571–1580.

Siewert, J.R., Böttcher, K., Stein, H.J. et al. (1998). Relevant prognostic factors in gastric cancer: ten-year results of the German gastric cancer study. *Ann Surg* 228: 449.

Singh, P.P. and Singh, S. (2013). Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Ann Oncol* 24: 1721–1730.

Smalley, S.R., Benedetti, J.K., Haller, D.G. et al. (2012). Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 30: 2327–2333.

Smith, D.D., Schwarz, R.R., and Schwarz, R.E. (2005). Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol* 23: 7114–7124.

Smyth, E.C., Verheij, M., Allum, W. et al. (2016). Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27: v38–v49.

Sobala, G., O'connor, H., Dewar, E. et al. (1993). Bile reflux and intestinal metaplasia in gastric mucosa. *J Clin Pathol* 46: 235–240.

Song, H., Ekheden, I.G., Zheng, Z. et al. (2015). Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. *BMJ* 351: h3867.

Songun, I., Putter, H., Kranenbarg, E.M. et al. (2010). Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 11: 439–449.

Stell, D., Carter, C., Stewart, I. et al. (1996). Prospective comparison of laparoscopy, ultrasonography and computed tomography in the staging of gastric cancer. *J Br Surg* 83: 1260–1262.

Stewart, H.L. (1967). Experimental alimentary tract cancer. *Natl Cancer Inst Monograph* 25: 199–217.

Straatman, J., van der Wielen, N., Cuesta, M.A. et al. (2015). Surgical techniques, open versus minimally invasive gastrectomy after chemotherapy (STOMACH trial): study protocol for a randomized controlled trial. *Trials* 16: 123.

Sung, H., Ferlay, J., Siegel, R.L. et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 71: 209–249.

Takahashi, M., Kokubo, T., Furukawa, F. et al. (1984). Effects of sodium chloride, saccharin, phenobarbital and aspirin on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. *GANN Jpn J Cancer Res* 75: 494–501.

Takahashi, Y., Takeuchi, T., Sakamoto, J. et al. (2003). The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: a prospective clinical study. *Gastric Cancer* 6: 142–145.

Talley, N.J., Zinsmeister, A.R., Weaver, A. et al. (1991). Gastric adenocarcinoma and Helicobacter pylori infection. *JNCI: J Natl Cancer Inst* 83: 1734–1739.

Tanioka, T., Waratchanont, R., Fukuyo, R. et al. (2020). Surgical and nutritional outcomes of laparoscopic proximal gastrectomy versus total gastrectomy: a meta-analysis. *Surg Endosc* 34: 1061–1069.

Tatematsu, M., Takahashi, M., Fukushima, S. et al. (1975). Effects in rats of sodium chloride on experimental gastric cancers induced by N-methyl-N′-nitro-N-nitrosoguanidine or 4-nitroquinoline-1-oxide. *J Natl Cancer Inst* 55: 101–106.

Thye, T., Burchard, G.D., Nilius, M. et al. (2003). Genomewide linkage analysis identifies polymorphism in the human interferon-γ receptor affecting Helicobacter pylori infection. *Am J Human Genet* 72: 448–453.

Tramacere, I., Negri, E., Pelucchi, C. et al. (2012). A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol* 23: 28–36.

Tsugane, S., Tei, Y., Takahashi, T. et al. (1994). Salty food intake and risk of Helicobacter pylori infection. *Jpn J Cancer Res* 85: 474–478.

U.S. Food and Drug Administration (2017). FDA grants accelerated approval to pembrolizumab for advanced gastric cancer. Available at (accessed 21 November 2022) https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577093.htm.

Uedo, N., Iishi, H., Tatsuta, M. et al. (2006). Longterm outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer* 9: 88–92.

Uemura, N., Okamoto, S., Yamamoto, S. et al. (2001). Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 345: 784–789.

Upchurch, E., Ragusa, M., and Cirocchi, R. (2018). Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction. *Cochrane Database Syst Rev* 5: Cd012506.

Valentini, V., Cellini, F., Minsky, B.D. et al. (2009). Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. *Radiother Oncol* 92: 176–183.

Wang, S., Freedman, N.D., Loftfield, E. et al. (2018). Alcohol consumption and risk of gastric cardia adenocarcinoma and gastric noncardia adenocarcinoma: a 16-year prospective analysis from the NIH-AARP diet and health cohort. *Int J Cancer* 143: 2749–2757.

Watanabe, H. (1978). Experimentally induced intestinal metaplasia in Wistar rats by X-ray irradiation. *Gastroenterology* 75: 796–799.

Watari, J., Das, K.K., Amenta, P.S. et al. (2008). Effect of eradication of Helicobacter pylori on the histology and cellular phenotype of gastric intestinal metaplasia. *Clin Gastroenterol Hepatol* 6: 409–417.

Weber, K., Reyes, C., Gagner, M. et al. (2003). Comparison of laparoscopic and open gastrectomy for malignant disease. *Surgical Endoscopy* 17.

Wei, Y., Yu, D., Li, Y. et al. (2018). Laparoscopic versus open gastrectomy for advanced gastric cancer: a meta-analysis based on high-quality retrospective studies and clinical randomized trials. *Clin Res Hepatol Gastroenterol* 42: 577–590.

Wilke, H., Muro, K., Van Cutsem, E. et al. (2014). Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 15: 1224–1235.

Willis, J., Lefterova, M.I., Artyomenko, A. et al. (2019). Validation of microsatellite instability detection using a comprehensive plasma-based genotyping panel. *Clin Cancer Res* 25: 7035–7045.

Wong, B., Lam, S., Ching, C. et al. (1999). Differential Helicobacter pylori infection rates in two contrasting gastric cancer risk regions of South China. *J Gastroenterol Hepatol* 14: 120–125.

Wong, B.C., Lam, S.K., Wong, W.M. et al. (2004). Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *Jama* 291: 187–194.

Wong, B.C., Zhang, L., Ma, J.L. et al. (2012). Effects of selective COX-2 inhibitor and Helicobacter pylori eradication on precancerous gastric lesions. *Gut* 61: 812–818.

Wu, C.Y., Wu, M.S., Kuo, K.N. et al. (2010). Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in Helicobacter pylori-infected patients. *J Clin Oncol* 28: 2952–2957.

Wynder, E.L., Kmet, J., Dungal, N. et al. (1963). An epidemiological investigation of gastric cancer. *Cancer* 16: 1461–1496.

Yamao, T., Kai, S., Kazami, A. et al. (1999). Tumor markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy in patients with advanced gastric cancer. *Jpn J Clin Oncol* 29: 550–555.

Ychou, M., Duffour, J., Kramar, A. et al. (2000). Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer. *Dis Markers* 16: 105–110.

Yokota, T., Kunii, Y., Teshima, S. et al. (1999). Significant prognostic factors in patients with node-negative gastric cancer. *Int Surg* 84: 331–336.

Yokota, T., Kunii, Y., Teshima, S. et al. (2000). Significant prognostic factors in patients with early gastric cancer. *Int Surg* 85: 286–290.

Yoon, J.M., Son, K.Y., Eom, C.S. et al. (2013). Pre-existing diabetes mellitus increases the risk of gastric cancer: a meta-analysis. *World J Gastroenterol* 19: 936–945.

Yu, J., Huang, C., Sun, Y. et al. (2019). Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. *Jama* 321: 1983–1992.

Yusefi, A.R., Bagheri Lankarani, K., Bastani, P. et al. (2018). Risk factors for gastric cancer: a systematic review. *Asian Pac J Cancer Prev* 19: 591–603.

Zhang, H., Sun, L.L., Meng, Y.L. et al. (2011). Survival trends in gastric cancer patients of Northeast China. *World J Gastroenterol* 17: 3257–3262.

Zhang, X., Li, M., Chen, S. et al. (2018). Endoscopic screening in Asian Countries is associated with reduced Gastric Cancer Mortality: a Meta-analysis and systematic review. *Gastroenterology* 155: 347–354.e9.

Zhao, L., Blot, W.J., Liu, W. et al. (1994). Familial predisposition to precancerous gastric lesions in a high-risk area of China. *Cancer Epidemiol Prev Biomark* 3: 461–464.

Zhao, Y. and Wang, C. (2018). Long-term clinical efficacy and perioperative safety of endoscopic submucosal dissection versus endoscopic mucosal resection for early gastric cancer: an Updated Meta-Analysis. *Biomed Res Int* 2018: 3152346.

Zhou, X.L., Xue, W.H., Ding, X.F. et al. (2017). Association between metformin and the risk of gastric cancer in patients with type 2 diabetes mellitus: a meta-analysis of cohort studies. *Oncotarget* 8: 55622–55631.

Zintzaras, E. (2006). Association of methylenetetrahydrofolate reductase (MTHFR) polymorphisms with genetic susceptibility to gastric cancer: a meta-analysis. *J Hum Genet* 51: 618–624.

8 Cancer of the Small Intestine

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[See Chapters 23, 24 and 26 for GIST, Neuroendocrine and Lymphoma tumour management details].

Introduction

The prevalence of cancer in the small intestine is low, with an incidence rate of 11 to 22 annual cases per one million people. Altogether, this entity occupies approximately three percent (Jemal 2008) of the working diagnoses in a general gastrointestinal (GI) oncology service (Bilimoria 2009). Yet, the incidence has been rising in an average rate of 2.3% each year in the past few years (Puccini et al. 2018). The low incidence is surprising, considering that the small intestine epithelium makes up more than 95% of the intestinal surface area. Moreover, unlike other GI cancers that include mostly adenocarcinoma, the histology of small intestine tumors is more diverse and comprises 45% adenocarcinoma, 30% neuroendocrine cancers, 15% lymphoma, and 10% sarcoma; those are mostly gastrointestinal stromal tumors (GIST). The prevalence of specific cancer types is influenced by location. While adenocarcinoma is the leading diagnosis in the duodenum, NET cancers are the leading diagnosis in the ileum. This chapter will focus mainly on adenocarcinoma of the small bowel while summarizing the current knowledge in the field and will provide directions for diagnosis and treatment.

Clinical Presentation and Diagnosis

The most frequent presenting symptom of small bowel tumors is abdominal pain**,** which is present **in 43 to 66** percent **of cases** (Dabaja et al. 2004; Halfdanarson et al. 2010). Because of the vagal innervation of the small bowel, the pain is often vague and **poorly** loca**lized**. Other symptoms **may include** GI bleeding, nausea, weight loss, bowel obstruction, and perforation. In most cases, symptoms are mild at first leading to a protracted medical evaluation and diagnosis.

The evaluation of the small bowel is challenging because of its length. Computerized tomography (CT) is a frequent tool used to evaluate non-specific abdominal pain with a sensitivity of 70–80 percent to small bowel tumors (Laurent 1991). CT enteroclysis is a more sensitive and hybrid technic in which in addition to a CT scan, the small intestine is filled with two types of contrast materials: Natural contrast media such as water and positive contrast material such as barium. Other means of direct visualization of the small intestine are wireless video capsule endoscopy and double-balloon enteroscopy.

Adenocarcinoma

Pathogenesis and Gene Analysis

Like colon cancer, it is believed that adenocarcinoma of the small bowel is a result of adenoma to carcinoma transition through a multistep accumulation of mutation**s**. In support of this assumption is the correlation between the size of adenoma found in Small Bowel Adenocarcinoma (SBA) to the risk of carcinoma in it. However, analysis of genome alteration suggests that small bowel adenocarcinoma is a unique entity. In a genomic analysis of GI adenocarcinoma from 7559 patients including 6353 patients with Colo-Rectal Cancer (CRC), 889 patients with Gastric Carcinoma, and 317 patients with small bowel tumors, it was demonstrated that the most frequent gene alteration in SBA were P53 (58%), KRAS (53%), **APC (26.8%),** SMAD4 (17.4%), PIK3CA (16.1%), CDKN2A (14.5%), ARID1A (12.3%). The frequency of these genes was distinctively different from both colonic and gastric adenocarcinoma. For example, APC gene alteration in colonic adenocarcinoma was found to be 75.9% in this analysis but a similar frequency of KRAS gene alternation was found at around 50%. The frequency of KRAS in gastric adenocarcinoma was only 14.2%. Microsatellite instability was found in 7.6% of SBA compared to 3.9% in CRC and 4% in GC. In addition, 9.5% of this cohort had a high tumor mutational burden of more than 20 mutations/Megabase. To note, 78% of the cohort patients had metastatic disease (Schrock 2017).

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Predisposition

The development of SBA can be facilitated by exposure to inflammation, carcinogen, or by germline gene alternation that leads to hereditary cancer syndromes.

The hallmark of chronic inflammation is cell damage and tissue repair resulting in accelerated accumulation of mutation and cell growth. This explains why patients with conditions that cause chronic inflammation are at high risk to develop SBA:

- Evidence (Frank and Shorey 1973) from the early 70s describes a high prevalence of SBA in patients with longstanding Crohn's disease (Munkholm et al. 1993). When comparing (Hoffman et al. 1977) Crohn's-mediated SBA to non-enteritis-related SBA, patients with Crohn's are younger, have a less successful cure, rise in a larger frequency in the ileum, and occur more frequently. Although CRC prevalence has been reduced in the last 30 years, small-bowel cancer in patients with Crohn's has not shown a significant reduction over the years and is still with a high relative risk of 33 (Canavan et al. 2006).
- Celiac disease is another cause of inflammation with a higher prevalence of SBA, (Rampertab et al. 2003) though these patients might have better overall survival than patients with non-celiac-associated SBA (Caio et al. 2019) adhering to a gluten-free diet might be a protective manner regarding the development of SBA in celiac patients (Green 2003).

Hereditary syndromes known to increase the risk for SBA include Hereditary Nonpolyposis Colorectal Cancer (HNPCC) also known as Lynch syndrome, Familial Adenomatous Polyposis (FAP), and Peutz-Jeghers. These three syndromes are autosomal dominant, meaning a person is born with a mutation in one allele and the other is lost or silenced subsequently in the tumor formed.

Of these, Lynch syndrome is the most common. In its hereditary form, a person is born with one allele of mismatch repair (MMR) proteins missing and the other is lost in the tumor. This results in a high level of microsatellite instability when a cell divides, leading to an increased number of non-homologous tumor mutations. The estimated lifetime risk to develop SBA with Lynch syndrome is **approximately** 4% (Koornstra et al. 2008) However, most SBA lacking expression of MMR (defined as dMMR) proteins do not have a genetic base (Suerink 2021).

In a cohort (Aparicio 2020) of 347 patients with small bowel adenocarcinoma, **approximately 20** percent had a predisposition condition including Crohn's disease (8.7%), Lynch syndrome (6.9%), familial adenomatosis polyposis (1.7%), Celiac disease (1.7%), and Peutz-Jeghers syndrome (0.6%). The high incidence of predisposing conditions suggests that patients presenting with SMA should be screened for occult conditions.

Predisposing conditions **occasionally correlate with specific genetic alterations in SBA** . For instance**,** patients with Lynch syndrome are more prone to show ATM, FGFR3, and FGFR1 gene alterations, and patients with Crohn's disease have more IDH1 mutations (Aparicio 2021).

Guidelines for Treatment of Local Disease

According to the Surveillance, Epidemiology, and End Results (SEER) Program, most patients are diagnosed with local disease including 10% stage I, 30% stage II, and 25% stage III. Only 35% are diagnosed with stage **IV disease** (Khosla 2022).

According to the NCCN, initial workup **should** include abdominal/pelvic/chest imaging (PET/FDG is not indicated), blood work **including tumor** markers (CEA/CA19-9), consider studies for celiac, and esophagogastroduodenoscopy (EGD) with Endoscopic Ultrasound (EUS) (if needed for better imaging). Treatment then differs according to findings:

- Resectable disease requires resection with en-bloc removal of local lymph nodes.
- Unresectable disease requires systemic treatment in combination with surgical (if needed – diversion or stent in case of obstruction**)**.

Surgical Treatment

- Surgery is the most important component of treatment to achieve cure in localized SBA and changes according to location. Periampullary and proximal duodenal cancer will often require pancreatoduodenectomy. Distal ileal tumors might require a right colectomy. Tumors in other locations will be treated with wide local segmented resection and lymph node dissection. However, the blood supply to the remaining bowel might limit the extent of the surgery, thus compromising the number of lymph node available to resect. **The optimal number of lymph nodes to be extracted is a matter of debate. A**ccording to the National Comprehensive Cancer Network (NCCN) guidelines**, the recommended minimum is the resection of at least eight lymph** nodes.

Systemic Treatment

- There are currently no randomized trials to guide the treatment approach after complete tumor resection. The global BALLAD phase III adjuvant trial is now recruiting and is aimed to evaluate the role of adjuvant chemotherapy (Journal of Clinical Oncology 2016 34:15_suppl, TPS4154-TPS4154, NCT04257461). Retrospective data regarding adjuvant therapy is inconsistent. **Many of the retrospective studies collected data from a single center, and do not show any benefit for adjuvant chemotherapy. However, this data is prone to major biases, as patients that received chemotherapy might be selected for adjuvant treatment due to bad prognostic factors** (Dabaja et al. 2004, Halfdanarson et al. 2010; Nakanoko 2015; Swartz 2007; Young 2016). A single matched analysis of 4747 patients from the national cancer database show**s** a significant advantage of adjuvant chemotherapy is achieved in patients with stage III disease (Ecker 2016).
- In the case of an irresectable disease, one small study (Onkendi 2012) has shown that neoadjuvant therapy

(chemotherapy with or without radiation) has converted the locally unresectable disease to a resectable disease with prolonged survival.

Adjuvant chemotherapy for 3-6 months is therefore indicated in cases **for patients post resection with a high pathological stage** – T3 with MSS (MicroSatellite Stable) or pMMR (hence – no deficiency in MMR proteins). Similar to colon cancer, the regimen of choice is either 5FU or the combination of 5FU and oxaliplatin, depending on the number of risk factors and age. Capecitabine is also possible instead of 5FU. In cases with no involvement of lymph nodes (N0), no presence of Perineural invasion (PNI) or Lymphovascular invasion (LVI) – observation is also acceptable. By extrapolation from CRC, patients with stage II MSI-H/dMMR have improved prognosis and therefore may not need adjuvant chemotherapy. **Based on publications in CRC, it is reasonable to consider incorporating Immune Checkpoint Inhibitors (ICI) treatment for high-risk patients. (Alvi, 2016)**

A recently published review (Khosla 2022) of acceptable treatments for SBA emphasizes the role of chemoradiation in the setting of duodenal disease, since these tend to local recurrence, although this treatment has not shown improvement in survival.

Surveillance includes physical examination and marker levels every 3–6 months for the first 2 years and then every 6–12 months until year 5. In addition, imaging every 6–12 months for the first 2 years followed by imaging every 12 months until year 5.

Metastatic Adenocarcinoma of the Small Intestine

Common metastatic sites of SBA are the liver and peritoneum. Peritoneal metastases are more common in jejunal and ileal primary.

Chemotherapy

- There are no randomized control trials that evaluated the efficacy of chemotherapy in metastatic small bowel adenocarcinoma. Retrospective and prospective phase II studies show that different types of chemotherapies can induce tumor regression: The efficacy of 5FU and oxaliplatin combination as first-line treatment was evaluated in two phase II trials. Overman et al. (Overman 2009) explored the efficacy of CAPOX regimen (Oxaliplatin and capecitabine) in 25 patients and found a response rate of 52% and median overall survival of 20.4 months. Xiang et al. (Xiang 2012) evaluated the efficacy of FOLFOX regimen (fluorouracil and oxaliplatin) in 33 patients and demonstrated a response rate of 48.5% with median overall survival of 15.2 months.
- One phase II study (McWilliams 2017) has shown that the addition of genotype-directed dosing UGT1A1 of Irinotecan (gCAPIRINOX) was feasible with favorable rates of hematologic toxicity in previously untreated SBA patients. Few retrospective studies evaluated the efficacy of irinotecan-based regimens in both first- and second-line showing a response rate of 9 to 25 percent and median overall survival of 9 to 10 months (Tsushima 2012; Zaanan 2010, 2011).
- Historically, the treatment approach to metastatic SBA was mainly influenced by the treatment paradigm of colon cancer. However, insights from genomic analysis supporting a more unique entity for SBA encouraged an effort to explore other drugs less effective in colon cancer. A small phase II trial (Overman 2018) evaluated the role of nab-paclitaxel in 10 patients showing an objective response in two patients supporting the ability of SBA to respond to agents that are not active in colon cancer. Another retrospective study (Aldrich et al. 2019) showed a response rate of 30% to second-line taxane-based therapy at various drug combinations including gemcitabine. These options are now included in the NCCN guidelines as an option for second-line treatment.

According to the NCCN, chemotherapy treatment for metastatic disease is based on 5FU/Capecitabine with or without oxaliplatin (according to the intensity of the intended regimen).

Immunotherapy

- The KeyNote 158 study (Marabelle 2020) included 19 patients with small bowel cancer, dMMR, and has shown response to pembrolizumab in 42% including complete response in **three** patient. In contrast, the ZEBRA trial (Pedersen 2021) a phase II study including 40 patients with previously treated SBA, did not achieve the expected endpoints with little response in the MSS group and 50% of the MSI-H achieving PR (Partial Response).
- One prospective study (Aydin 2017) including 28 patients with advanced SBA showed that second-line treatment with the addition of Bevacizumab was more effective than chemotherapy alone, though results were not statistically significant. And yet, in a meta-analysis (Vergara et al. 2019) combining this trial and another phase 2 study (Gulhati 2017) they have demonstrated an improvement in the overall survival for patients with added Bevacizumab to chemotherapy.
- Panitumumab (an anti-EGFR protein) has shown no clinical activity in a phase II trial (Gulhati 2018) although was well tolerated.

The guidelines state that in addition to chemotherapy, patients should receive either Bevacizumab (efficacy is yet to be proven, although it has shown safety) in pMMR cases or Immune Checkpoint Inhibitors (ICI) exclusively in dMMR patients, comprised of Nivolumab with Ipilimumab or pembrolizumab.

Although not part of the guidelines, treatment with pembrolizumab in metastatic SBA should remain an option even when unknown MSI status, or If MSS, according to the ZEBRA trial (Pedersen 2021). The rationale is led by the hypothesis that metastatic SBA patients have a high programmed death-ligand 1 (PD-L1) expression.

Surgical Treatment

- Metastasectomy might be considered in patients with single metastasis to visceral organs (Adam 2006).

- Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for peritoneal metastases has also been shown (Liu 2018) to achieve prolonged survival for selected patients, as shown in a series of 152 patients.

Regarding biological treatment – according to the available data, there seems to be no clear benefit for monotherapy with panitumumab or cetuximab, in metastatic SBA. Albeit, the addition of cetuximab to chemotherapy might be safe and well-tolerated, with efficacy yet to be proven (Mazlom et al. 2021).

Prognosis

Small Bowel Adenocarcinoma is lethal in its advanced stages (Locher 2018). Due to its rarity, little is known about effective treatment. A nomogram (Zhu 2022) based on the SEER program has evaluated the following characteristics as bad prognostic features for three-year survival in metastatic SBA:

> Advanced age (>76 years), primary duodenal disease, large tumors with high tumor grade, primary tumor resection, and chemotherapy treatment.

Other less common pathologies of the small bowel include Neuroendocrine tumors, Lymphomas, Sarcomas, and metastasis to the small intestine. Hereby is a short brief of these pathologies, a more elaborate description will take place in the relevant chapters.

NET

Pathogenesis

Neuroendocrine tumors of the small intestine are most often indolent tumors once called carcinoid, implying that they are cancer-like but are not cancerous. However, though they are slow-growing, they frequently do send metastasis and are lethal in many cases. The ability of these tumors to produce hormones can cause “carcinoid syndrome” which characteristics differ according to the mediator, mostly including flushing and diarrhea (Kulke and Mayer 1999).

These tumors are less aggressive than other malignancies of the GI tract. They originate from neuroendocrine cells and can be divided into functional tumors**,** which are capable of producing hormones, and non-functional tumors. Tumors can metastasi**ze** even if the primary tumor is small (Rorstad 2005).

Treatment for Local Disease

A wide en-bloc resection of local disease is recommended. This includes the resection of the mesentery and lymph nodes (Loftus and van Heerden 1995). Due to the high incidence of a second GI malignancy in patients with SB-NET, patients should undergo an entire GI **and possibly GU** evaluation prior to surgery and have an intraoperative assessment (Prommegger 2014).

Treatment for Metastatic Disease

Treatment should include resection, when possible, even with liver metastasis, although surgery in patients with carcinoid syndrome might be hazardous. Systemic treatment with somatostatin analogs might provide long-term relief of symptoms in addition to having an antiproliferative effect (Scott and Howe 2020).

Lymphoma

Lymphomas to the GI tract are most commonly non-Hodgkin and have better prognosis than lymphomas of lymph node origin. Nonetheless, treatment is similar to standard extranodal lymphoma treatment, with the exclusion of surgery in cases of small bowel obstruction (Beaton et al. 2012).

GIST

The most common sarcomas of the small bowel are gastrointestinal stromal tumors (GIST). Non-GIST sarcomas include leiomyosarcoma, fibrosarcoma, liposarcoma, Kaposi sarcoma, and angiosarcoma. The molecular hallmark of GIST is a mutation in either KIT or PDGFRA gene. While the mutations cause resistance to chemotherapy, they can be targeted by Imatinib leading to prolonged tumor control (Kang et al. 2015).

Surgical treatments include en-bloc resection. Mesenteric lymphadenectomy is not obligatory.

Metastasis to the Small Intestine

The small intestine is rarely involved in metastasis from other origins. The most common sites of hematogenous spread include melanoma, breast, and lung cancer (Kadakia et al. 1992) Treatment is mostly palliative.

Key Take Home Messages

- Small bowel cancer is rare, with a non-unique pattern of presentation – mostly vague abdominal pain. Diagnosis can be complicated due to low visualization abilities of the small bowel; therefore, early disease diagnosis is uncommon.
- Adenocarcinoma is the most common type of cancer in the small bowel, though there are rising portions of NET in the past few years. Other types are lymphoma and sarcoma. Adenocarcinoma is believed to evolve from an adenoma, similarly to CRC, though gene analysis suggests that small bowel adenocarcinoma is a unique entity. Microsatellite instability was found in a higher percentage of metastatic SBA in comparison to metastatic CRC.
- Patients with inflammation (i.e. Crohn’s and celiac diseases) are at a higher risk of developing SBA, suggesting screening in these patients. Other common predispositions

are hereditary syndromes such as Lynch, FAP, and Peutz-Jegher. One study showed almost 20% of patients with SBA had a predisposition condition, raising the question regarding the screening of patients presenting with SBA for occult conditions.

- Treatment in stages I-III is primarily reliant on surgery, with scarce studies showing benefits for adjuvant therapy, mostly retrospective. The common practice is chemotherapy for stage III disease, comprising of oxaliplatin-based combinations.
- Treatment for metastatic disease has very little evidence and is mostly based on relevant treatment for CRC. Mostly oxaliplatin-based in combination with Immune Checkpoint Inhibitors.

Knowledge Gaps

- It is suggested that chronic inflammation is a strong risk factor for the development of SBA, but it has not been proven and screening guidelines are rather deficient. Further investigation regarding relevant populations and appropriate screening methods should take place.
- There are many gaps in the evidence for the need for systemic treatment for advanced disease. Prospective studies should take place to fill these gaps.
- Patients with unresectable disease are and no doubt in need of systemic treatment, yet there is little evidence regarding the benefits of chemotherapy, and the addition of more advanced treatments such as biological or immunological regimens.

National Evidence-based Guideline

- NIH patient guide: https://www.cancer.gov/types/small-intestine/patient/small-intestine-treatment-pdq
- NCCN: https://jnccn.org/view/journals/jnccn/17/9/article-p1109.xml

References

Adam, R., Chiche L., Aloia T., et al. (2006). Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg* 244: 524–535.

Aldrich, J.D., Raghav, K.P.S., Varadhachary, G.R. et al. (2019). Retrospective analysis of taxane-based therapy in small bowel Adenocarcinoma. *Oncologist* 24: e384–e386.

Aparicio, T., Henriques J., Manfredi S., et al. (2020). Small bowel adenocarcinoma: results from a nationwide prospective ARCAD-NADEGE cohort study of 347 patients. *Int J Cancer* 147: 967–977.

Aparicio, T., Svrcek M., Henriques J. et al. (2021). Panel gene profiling of small bowel adenocarcinoma: results from the NADEGE prospective cohort. *Int J Cancer* 148: 1731–1742.

Aydin, D. Ali Sendur M., Kefeli U., et al. (2017). Evaluation of Bevacizumab in advanced small bowel adenocarcinoma. *Clin Colorectal Cancer* 16: 78–83.

Beaton, C., Davies, M., and Beynon, J. (2012). The management of primary small bowel and colon lymphoma–a review. *Int J Colorectal Dis* 27: 555–563.

Bilimoria, K.Y. Bentrem D.J., Wayne J.D et al. (2009). Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. *Ann Surg* 249: 63–71.

Caio, G., Volta, U., Ursini, F. et al. (2019). Small bowel adenocarcinoma as a complication of celiac disease: clinical and diagnostic features. *BMC Gastroenterol* 19: 45.

Canavan, C., Abrams, K.R., and Mayberry, J. (2006). Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 23: 1097–1104.

Dabaja, B.S., Suki, D., Pro, B. et al. (2004). Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. *Cancer* 101: 518–526.

Ecker, B.L. McMillan M.T., Datta J.,. et al. (2016). Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: a propensity score-matched analysis. *Cancer* 122: 693–701.

Frank, J.D. and Shorey, B.A. (1973). Adenocarcinoma of the small bowel as a complication of Crohn's disease. *Gut* 14: 120–124.

Green, P.H.R. Fleischauer A.T., Bhagat G. et al. (2003). Risk of malignancy in patients with celiac disease. *Am J Med* 115: 191–195.

Gulhati, Raghav K., Shroff R.T., et al. (2017). Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of vater: a single-center, open-label, phase 2 study. *Cancer* 123: 1011–1017.

Gulhati, P. Raghav K., Shroff R. et al. (2018). Phase II study of Panitumumab in RAS Wild-type metastatic Adenocarcinoma of small bowel or Ampulla of Vater. *Oncologist* 23: 277–e26.

Halfdanarson, T.R., McWilliams, R.R., Donohue, J.H., and Quevedo, J.F. (2010). A single-institution experience with 491 cases of small bowel adenocarcinoma. *Am J Surg* 199: 797–803.

Hoffman, J.P., Taft, D.A., Wheelis, R.F., and Walker, J.H. (1977). Adenocarcinoma in regional enteritis of the small intestine. *Arch Surg* 112: 606–611.

Jemal, A. Siegel R., Ward E., et al. (2008). Cancer statistics. *CA Cancer J Clin* 58: 71–96.

Kadakia, S.C., Parker, A., and Canales, L. (1992). Metastatic tumors to the upper gastrointestinal tract: endoscopic experience. *Am J Gastroenterol* 87: 1418–1423.

Kang, W., Zhu, C., Yu, J. et al. (2015). KIT gene mutations in gastrointestinal stromal tumor. *Front Biosci Landmark Ed.* 20: 919–926.

Khosla, D. Dey Madan R. T.+ et al. (2022). Small bowel adenocarcinoma: an overview. *World J Gastrointest Oncol* 14: 413–422.

Koornstra, J.J., Kleibeuker, J.H., and Vasen, H.F.A. (2008). Small-bowel cancer in Lynch syndrome: is it time for surveillance? *Lancet Oncol* 9: 901–905.

Kulke, M.H. and Mayer, R.J. (1999). Carcinoid tumors. *N Engl J Med* 340: 858–868.

Laurent, F., Raynaud M., Biset J.M. et al. (1991). Diagnosis and categorization of small bowel neoplasms: role of computed tomography. *Gastrointest Radiol* 16: 115–119.

Liu, Y., Yonemura Y., Levine E.A. et al. (2018). Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for peritoneal metastases from a small bowel Adenocarcinoma: multi-institutional experience. *Ann Surg Oncol* 25: 1184–1192.

Locher, C. Batumona B., Afchain P. et al. (2018). Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). *Dig Liver Dis* 50: 15–19.

Loftus, J.P. and van Heerden, J.A. (1995). Surgical management of gastrointestinal carcinoid tumors. *Adv Surg* 28: 317–336.

Marabelle, A., Le D.T., Ascierto P.A et al. (2020). Efficacy of Pembrolizumab in patients with Noncolorectal high microsatellite instability/Mismatch repair-deficient cancer: results from the Phase II KEYNOTE-158 study. *J Clin Oncol* 38: 1–10.

Mazlom, H., Teuwen, L.-A., and Peeters, M. (2021). Management of small bowel adenocarcinoma: making the most of the available evidence to inform routine practice. *Curr Opin Oncol* 33: 368–371.

McWilliams, R.R. et al. (2017). North Central Cancer Treatment Group N0543 (Alliance): a phase 2 trial of pharmacogenetic-based dosing of irinotecan, oxaliplatin, and capecitabine as first-line therapy for patients with advanced small bowel adenocarcinoma. *Cancer* 123: 3494–3501.

Munkholm, P., Langholz, E., Davidsen, M., and Binder, V. (1993). Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 105: 1716–1723.

Nakanoko, T., Koga T., Taketani K., et al. (2015). Characteristics and treatment strategies for small bowel Adenocarcinoma in Advanced-stage cases. *Anticancer Res* 35: 4135–4138.

Onkendi, E.O., Boostrom S.B., Sarr M.G. et al. (2012). Neoadjuvant treatment of duodenal adenocarcinoma: a rescue strategy. *J Gastrointest Surg* 16: 320–324.

Overman, M.J., Varadhachary G.R., Kopetz, S. et al. (2009). Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. *J Clin Oncol* 27: 2598–2603.

Overman, M.J., Adam L., Raghav K. et al. (2018). Phase II study of nab-paclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. *Ann Oncol Off J Eur Soc Med Oncol* 29: 139–144.

Pedersen, K.S., Foster N.R., Overman M.J., et al. (2021). ZEBRA: a multicenter phase II study of Pembrolizumab in patients with advanced Small-Bowel Adenocarcinoma. *Clin Cancer Res* 27: 3641–3648.

Prommegger, R., Ensinger C., Steiner P. et al. (2014). Neuroendocrine tumors and second primary malignancy–a relationship with clinical impact? *Anticancer Res* 24: 1049–1051.

Puccini, A., Battaglin, F., and Lenz, H.-J. (2018). Management of advanced small bowel cancer. *Curr Treat Options Oncol* 19: 69.

Rampertab, S.D., Forde, K.A., and Green, P.H.R. (2003). Small bowel neoplasia in coeliac disease. *Gut* 52: 1211–1214.

Rorstad, O. (2005). Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol* 89: 151–160.

Schrock, A.B., Devoe C.E., McWilliams R., et al. (2017). Genomic Profiling of Small-Bowel Adenocarcinoma. *JAMA Oncol* 3: 1546–1553.

Scott, A.T. and Howe, J.R. (2020). Management of small bowel neuroendocrine tumors. *Surg Oncol Clin N Am* 29: 223–241.

Suerink, M., Kilinc G., Terlouw D. et al. (2021). Prevalence of mismatch repair deficiency and Lynch syndrome in a cohort of unselected small bowel adenocarcinomas. *J Clin Pathol* 74: 724–729.

Swartz, M.J., Hughes M.A., Frassica D.A et al. (2007). Adjuvant concurrent chemoradiation for node-positive adenocarcinoma of the duodenum. *Arch Surg* 142: 285–288.

Tsushima, T., Taguri M., Honma Y. et al. (2012). Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. *Oncologist* 17: 1163–1170.

Vergara, J.P., Sacdalan, D.B.L., Amurao-Amante, M., and Sacdalan, D.L. (2019). Bevacizumab in metastatic small-bowel adenocarcinoma: a systematic review and meta-analysis. *Rare Tumors* 11: 2036361318825413.

Xiang, X.J. Liu Y.W., Zhang L.,. et al. (2012). A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. *Anticancer Drugs* 23: 561–566.

Young, J.I., Mongoue-Tchokote S., Weighard N et al. (2016). Treatment and survival of Small-bowel Adenocarcinoma in the United States: a comparison with colon cancer. *Dis Colon Rectum* 59: 306–315.

Zaanan, A., Costes L., Gauthier M., et al. (2010). Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. *Ann Oncol Off J Eur Soc Med Oncol* 21: 1786–1793.

Zaanan, A., Gauthier M., Malka D., et al. (2011). Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. *Cancer* 117: 1422–1428.

Zhu, H., Zhao S., Zhao T. et al. (2022). Development and validation of prognostic nomograms for patients with metastatic small bowel adenocarcinoma: a retrospective cohort study. *Sci Rep* 12: 5983.

Section II Colorectal and Anal Cancer

9 Epidemiology, Microbiome, and Risk Factors Involved in Carcinogenesis of Colorectal Cancer

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[Elements of Colorectal Cancer Epidemiology, Risk Factors, and Microbiome as also discussed in Chapter 1]
[Aspects of Nutrition in cancer and cancer prevention are also discussed in Chapter 1 and Chapter 29]

Epidemiology

Colorectal cancer (CRC) is the fourth commonest cancer-related death. Colorectal cancer accounts for approximately 10% of cancer mortality in the West, making it the second deadliest malignancy in the UK, the USA, and Australasia, after lung cancer. Furthermore, at a global level there is evidence the mortality has increased globally by approximately 25% over the last two decades. The reasons for this are in part due increased ageing in the population, decline of healthy diets and exercise with concomitant increases in obesity as well as consumption of more alcohol and cigarette use. This is particularly the case in Eastern Europe, South America, South Eastern and Central Asia where red meat consumption remains high. There is considerable heterogeneity of incidence, as populations with a high human development index (HDA), have CRC rates, which are decreasing from the very high levels in some select countries. There is considerable debate as to the factors for this variation, but CRC screening programs and polypectomy, may be in part responsible.

Even in hereditary cancer syndromes, such as Lynch syndrome, with multisite lesions, colorectal cancer is now the main site of presentation. This is a major change to the presentation of Lynch syndrome where 50 years ago gastric cancer predominated. Despite the transformation of the therapeutic landscape for both primary and metastatic colorectal cancer, there has been only a limited increase in cure rates and long-term survival (Dekker et al. 2019, Patel et al. 2022, Sinicrope 2022).

There is a slight predominance of cancers in males with a female/male ratio of 0.9/1. In addition, 75% of rectal cancer and 80% of colonic cancer occurs > 60 years of age. There is also a predominance in more-developed countries such as North America, Europe, and Australasia compared with less developed countries of Africa, most of Asia, Latin America, and the Pacific islands.

There has been an increase in the number of early-onset CRC (CRC occurring before 50 years) especially in the Australia, Europe, Japan, Taiwan, and the USA.

Microbiome

It is estimated that for every human cell there is at least one bacterial cell. In the colon the microbiota is approximately 10^{13} to 10^{14} microbes and approximately 50–60% of the dry weight of stool is from the microbiota (Wong and Yu 2019). Organisms are present throughout the alimentary tract, but the greatest variety and number are found in the colon. Normal microbiota is essentially for digestion of food through fermentation, provision of key nutrients and energy, stimulating colonic contraction, suppressing growth of parasites, maintaining immunity, and hostile organisms as well as secreting factors and short chain Fatty acids that enhance mucosal growth. Conversely dysbiosis is associated with many gastrointestinal diseases ranging from bloating predominant irritable bowel disease, initiation of inflammatory bowel disease, and most importantly the catalysis of colorectal cancer. Several organisms in particular are linked with colorectal cancer including Streptococcus bovis (*S. bovis*), Streptococcus gallolyticus (*S. Gallolyticus*), Escherichia coli (*E. Coli*), Enterococcus faecalis (*E. faecalis*), Enterotoxigenic Bacteroides fragiles (ETBF), and oral Fusobacterium nucleatum (*F. nucleatum*). It is thought that these organisms cause inflammation which then acts to increase cell turnover, damage cells especially the DNA in stem cells and drive the growth of aberrant crypts in the hospital environment.

The key issue with microbiota is to have as diverse a spectrum of bacteria, fungi, and viruses as possible, as this favors colorectal health. There is evidence that highly variable vegetarian diets or mixed vegetarian and pescatarian diets are strongly correlated with the widest spectrum of microbiota. Conversely, chronic inflammation such as occurs in inflammatory bowel disease decreases microbiotic diversity resulting in procarcinogenetic dysbiosis.

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Risk Factors

There are major contributions from both genetic and environmental factors to the aetiology of colorectal cancer (Song et al. 2015).

5–10% of colorectal cancer incidence in the west can be attributed to those who have classical hereditary colorectal cancer syndromes. The commonest of these are, the Lynch syndrome, Familial Adenomatosis Polyposis syndrome, MUTYH syndrome, Peutz Jeghers syndrome, serrated polyposis, and juvenile polyposis.

1% of colorectal cancer is associated with chronic colitis due to either ulcerative colitis or Crohn's Disease.

The remaining ~ 90% of colorectal cancer can be attributed at least in part to modifiable risk, many of the predisposing environmental factors are mentioned above. These cancers are very amenable to screening and surveillance programs as they arise from the adenoma-carcinoma sequence.

There are also protective factors including whole grains, fresh fruits, vegetables, calcium in milk, and vitamin D predominantly from cruciferous vegetable and oily fish. In addition, 30 mins of daily moderate exercise also mitigates risk. Low dose aspirin intake is associated with a 20–45% reduced incidence depending on the duration of salicylate therapy. Statins and hormone replacement therapy in women seem to have a more modest chemo preventive effect.

These modifiable factors are thought to change the risk of colorectal cancer by a relative risk of 1.8 to 0.5.

Key Take Home Messages

1 Most colorectal cancers can be delayed or even prevented with adherence to healthy lifestyle factors with zero tolerance of cigarette smoke.
2 Obesity showed be handled by progressive escalation of interactions.
3 Maintenance of healthy microbiota is essential for colonic health.
4 Low dose aspirin is useful as an adjunct in a proportion of those with known diseases that predispose colorectal cancer.

Areas Needing Further Research

1 The optimal microbiota regimen to ingest to prevent colorectal cancer.
2 The long-term value of low dose aspirin in primary prevention.
3 Capsule endoscopy sampling technology.

Trusted Websites for Further Reading

https://www.nih.gov/news-events/news-releases/new-tool-developed-predict-colorectal-cancer-risk

https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/colorectal-cancer

References

Dekker, E., Tanis, P.J., Vleugels, J.L.A. et al. (2019 October 19). Colorectal cancer. *Lancet* 394 (10207): 1467–1480.

Patel, S.G., Karlitz, J.J., Yen, T. et al. (2022 March). The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol* 7 (3): 262–274.

Sinicrope, F.A. (2022 April 21). Increasing incidence of Early-Onset colorectal cancer. *N Engl J Med* 386 (16): 1547–1558.

Song, M., Garrett, W.S., and Chan, A.T. (2015 May). Nutrients, foods, and colorectal cancer prevention. *Gastroenterology* 148 (6): 1244–1260.

Wong, S.H. and Yu, J. (2019 November). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol* 16 (11): 690–704.

10 Genomics, Histopathology, and Molecular Pathology of Sporadic and Hereditary Colorectal Cancer

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Introduction

Colorectal cancer (CRC) is the third commonest cancer (after lung and breast), and is the second leading cause of cancer-related mortality (Bray et al. 2018). Advances in our understanding of pathophysiology and the adoption of modern detection and treatment modalities have led to continuous improvement in outcomes in the Western world (Arnold et al. 2017). Worryingly however, these gains look set to be overtaken by the rising incidence of CRC in developing countries. The growing incidence of CRC in young patients is also likely to add further complexity to screening and treatment decisions (Gandhi et al. 2017). The majority of CRC cases are sporadic, with only 5–10% linked to a hereditary predisposition syndrome (Syngal et al. 2015). However, these rare syndromes have helped us understand the molecular mechanisms of CRC initiation and progression. In the past few years, considerable effort has been invested to understand the genetic and transcriptomic profiles of CRC, adding to our current knowledge of this heterogeneous disease. Three main pathways have been implicated, namely chromosomal instability (CIN), microsatellite instability (MSI), and the serrated neoplasia pathway. In this chapter, we will begin by reviewing the colonic microarchitecture in homeostasis. We will then see how this fine balance gets affected by the pathways mentioned above and highlight how these tumors lend themselves to specific therapeutic options.

Role of Intestinal Stem Cells in Tumor Formation

The intestinal lining is a rapidly self-renewing epithelial monolayer whose growth is fueled by intestinal stem cells (ISCs) that reside at the bottom of the crypts, which are invaginations of the epithelial layer (Figure 1) (Radtke and Clevers 2005). In health, these long-lived ISCs give rise to transit-amplifying cells, which produce the short-lived differentiated cells of the epithelium. ISCs that populate a crypt compete with each other for space (Snippert et al. 2014). Through a process of neutral drift, over time, a particular ISC will dominate the whole stem cell compartment (becomes fixed). This process is greatly speeded in the presence of a mutation conferring a competitive advantage (Vermeulen et al. 2013) or through other non-mutagenic modulators such as diet and ageing (Bruens et al. 2020; Nalapareddy et al. 2017).

As they are long-lived and display high levels of Wnt activation (like CRC cells), ISCs have been postulated to be the cell of origin of intestinal tumors. Indeed, using a genetically engineered mouse model, Barker and colleagues showed that targeted deletion of the *Adenomatous Polyposis Coli* (*APC*) gene in ISCs led to tumor formation within days (Barker et al. 2009), demonstrating that loss of this tumor suppressor gene and Wnt-regulator in ISCs was sufficient for tumor initiation. Similarly, activating mutations in *CTNNB1* (ß-catenin, an important activator of the Wnt pathway) in ISCs were found to lead to tumorigenesis (Sangiorgi and Capecchi 2008; Zhu et al. 2009).

In spite of this, some evidence in humans points away from this "bottom up" model. When sporadic adenomas were micro-dissected, the areas of dysplasia were found mostly to be on the luminal surface of the colon with normal crypt morphology underneath and only cells at the top of the crypts had mutations in *APC* (Shih et al. 2001). More recently, a multiomics approach has begun to shed light on this debate. Using a combination of histology, sequencing, and transcriptomic profiling, Chen and colleagues identified at least two different transcriptional pathways for human colorectal polyp formation and suggested that conventional adenomas originate from ISCs (bottom-up pathway) while serrated polyps originate from more differentiated cells (top-down pathway) (Chen et al. 2021).

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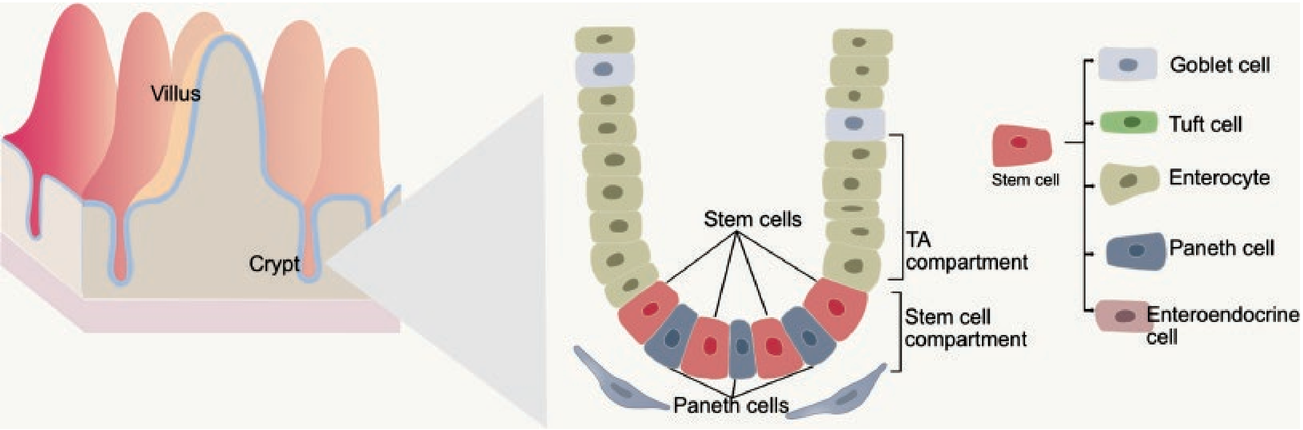

Figure 1 On edge view of a small intestinal crypt. Colonic architecture is similar with two exceptions, which are the absence of villi and Paneth cells. TA: transit-amplifying.

Conventional (Or Chromosomal Instability) Pathway

The majority (70–90%) of CRC arise from the conventional adenoma-carcinoma pathway. This involves the stepwise accumulation of mutations, typically starting with loss of function mutations in *APC* (Fearon and Vogelstein 1990).

APC is a Key Regulator of Wnt Signaling

The product of the tumor suppressor gene *APC* is 2,843 amino acid long. It is a key regulator of the Wnt pathway, which is crucial for cellular proliferation and organ development (Cadigan and Nusse 1997). In the absence of Wnt ligands, APC forms a destruction complex with Axin, Casein-kinase I and GSK-3ß, which targets the effector ß-catenin for proteasomal degradation by phosphorylating it (Figure 2) (Aberle et al. 1997; Orford et al. 1997). In contrast, in the presence of Wnt ligands, ß-catenin is able to translocate to the nucleus, where it binds to members of the T-cell factor (TCF)-lymphoid enhancer factor (LEF) family of transcription factors, which regulate several crucial genes such as the proto-oncogene c-myc and the cell cycle regular cyclin-D1 (He et al. 1998; Tetsu and McCormick 1999). Therefore, overactivation of the Wnt pathway and epithelial hyperproliferation result from loss of function mutations in *APC* or gain of function mutations in *CTNNB1*.

APC Contributes to Chromosomal Stability

As well as single nucleotide variations and small insertions and deletions (indels), large scale chromosomal rearrangements and copy number changes are common in CRC. This chromosomal instability is thought to result from defective cell division during mitosis, and a role for *APC* in this process has been suggested. Fodde and colleagues showed that *APC*-mutant mouse embryonic stem cells containing the Min (*multiple intestinal neoplasia*) or *Apc1638T* alleles showed extensive chromosome and spindle aberrations (Fodde et al. 2001). Subsequent work has shown that APC localizes to the ends of microtubules in kinetochores during mitosis, shedding light on the mechanism of chromosomal instability following the loss of APC (Kaplan et al. 2001).

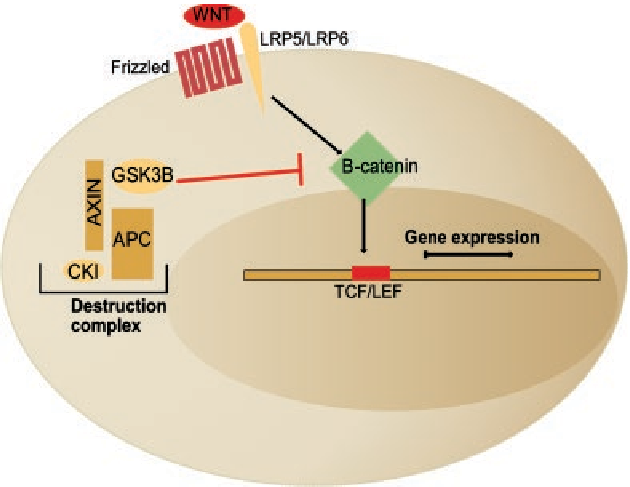

Figure 2 Schematic representation of Wnt signaling pathway.

Sequence of Events in CIN

The multistep model of colorectal carcinogenesis proposes that mutations in *APC* occur early in the development of colorectal polyps (Figure 3) (Fearon and Vogelstein 1990; Jones et al. 2008). Indeed, 60–80% of sporadic CRCs have somatic mutations in *APC* (Figure 4) (Narayan and Roy 2003). These

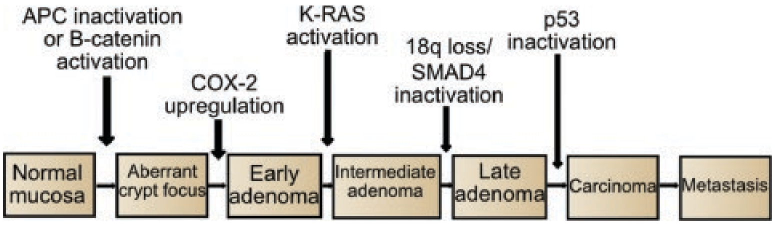

Figure 3 Proposed sequence of events in the conventional adenoma-carcinoma sequence.

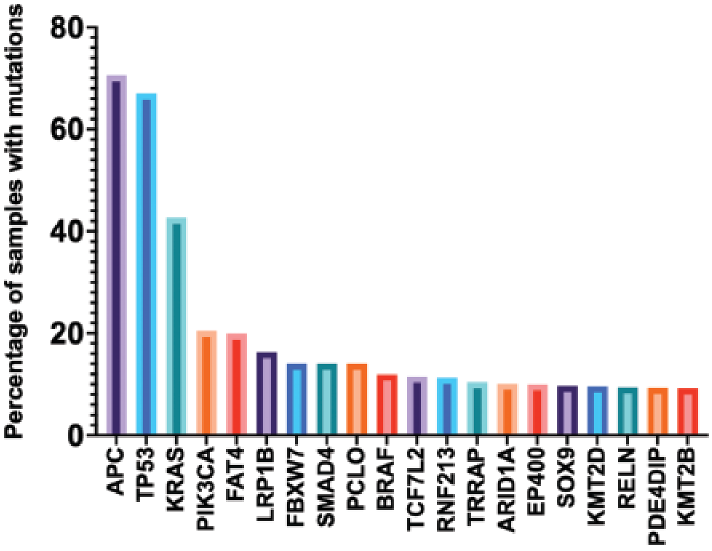

Figure 4 Top 20 cancer driver mutations in colorectal adenocarcinoma, ranked in order of decreasing frequency. Data extracted from 11 published studies comprising 3619 samples (Source: cBioportal).

mutations in *APC* tend to cluster between codons 1286 and 1513, in a region called the mutational cluster region (MCR) (Mori et al. 1992).

This is followed by mutations in *KRAS*, which is an important activator of the *RAF/MAPK*, *JNK* and *PI3-K* pathways. Mutations in *KRAS* occur in up to 68% of sporadic CRCs and activating mutations lead to constitutive activation of the downstream pathways, promoting cell proliferation, and survival independent of the EGFR receptor (Armaghany et al. 2012; McLellan et al. 1993). Interestingly, most activating mutations in *KRAS* are point mutations at codons 12, 13, and 35, which has led to much effort in finding specific KRAS inhibitors (Jiri et al. 2022).

Mutations in *TP53*, which is a protein that induces G1 cell-cycle arrest and induces cell death (apoptosis) in the presence of DNA damage, are thought to occur during the transition from adenoma to invasive cancer (Armaghany et al. 2012). *TP53* mutated CRCs have been shown to have a worse prognosis compared to those with wild-type CRC, and is associated with resistance to radiotherapy in patients with rectal cancer (Munro et al. 2005).

Up to 70% of CRCs demonstrate loss of chromosome *18q* and these are associated with a poorer prognosis (Popat and Houlston 2005). This has led to the suggestion that there might be tumor suppressor genes at that locus which strongly influence survival. *SMAD4*, which is coded by a gene located at chromosome *18q21.1*, is an important tumor suppressor which mediates the intracellular signaling of the TGF-beta pathway (Zhou et al. 1998). Tanaka and colleagues demonstrated that *18q* loss and *SMAD4* expression were correlated, and hypothesized that *SMAD4* is the tumor suppressor gene whose loss is critical during *18q* loss (Tanaka et al. 2006). Indeed, loss of *SMAD4* is associated with more aggressive disease and with resistance to chemotherapy (Wasserman et al. 2019).

Familial Adenomatous Polyposis Syndrome

Familial adenomatous polyposis (FAP) syndrome is an autosomal dominant inherited condition that predisposes to CRC. Although it only contributes about 1% of all CRC cases, studies of FAP have shed considerable light on the process of tumor formation in colonic epithelium. FAP occurs in 1 in 8,300 to 14 000 patients, with 50% of those developing colorectal adenomas by the age of 16 years (Kim and Bodmer 2021). The lifetime risk of CRC in patients with FAP exceeds 90% if left untreated and there are also increased risks of duodenal cancer, pancreatic cancer, medulloblastoma, papillary thyroid cancer, and hepatoblastoma (Stoffel and Boland 2015).

Patients with FAP carry germline mutations in *APC*. In spite of its autosomal dominant inheritance, 30% of patients with germline *APC* mutations have no family history and are presumed to have de novo *APC* mutations (Bisgaard et al. 1994). Benign extracolonic manifestations of FAP include epidermoid cysts, congenital hypertrophy of the retinal pigment epithelium (CHRPE) and osteomas (Kim and Bodmer 2021; Morton et al. 2005).

The phenotype displayed (age of onset, type, and number of intestinal polyps and extracolonic polyps) has been shown to correlate with the type and location of *APC* mutation incurred. Mutations located towards the proximal portion of the protein (before codon 1249) are associated with fewer than 1000 polyps (sparse polyposis), while those between codon 1250 and 1330 with >5000 polyps (profuse polyposis) (Friedl et al. 2001; Lal and Gallinger 2000; Leppert et al. 1990). Similarly, mutations that are located very close to the N-terminus of the protein or distal to codon 1578 lead to a milder phenotype with a reduced number of polyps (less than 100) and an age of onset that is 10–15 years later than in classical FAP, in a condition called attenuated FAP (AFAP) (Spirio et al. 1992).

The diagnosis of FAP relies primarily on the number and history of colorectal adenomas. Patients with 100 or more polyps, or with fewer than 100 polyps but with a family history of FAP are clinically diagnosed with FAP. A clinical diagnosis of FAP is usually followed by sequencing of *APC* to identify the pathogenic variant. As they are at risk for duodenal polyposis and cancer, patients with confirmed FAP are also recommended a screening gastroscopy from the age of 25 years, and then at regular intervals according to the Spigelman classification (Spigelman et al. 1989). Patients with a first-degree relative with a clinical diagnosis of FAP are considered at risk and are offered regular surveillance colonoscopies starting at 12–14 years of age (Monahan et al. 2020).

The management of FAP is mainly surgical, with prophylactic surgery being the treatment of choice. Non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac have been shown to induce polyp regression in some patients but this effect was not sustained following treatment cessation (Giardiello et al. 1993). Due to the high penetrance of colorectal cancer in patients with FAP, prophylactic surgery is recommended shortly after diagnosis. The principles of surgery in these patients are the removal of all at-risk colorectal mucosa and restoration of bowel continuity if it is safe to do so (Setti-Carraro and Nicholls 1996). Surgical options include total colectomy and ileorectal anastomosis (in patients with limited rectal polyp burden and willing for regular endoscopic surveillance), proctocolectomy and ileal pouch-anal anastomosis, total proctocolectomy and end ileostomy or proctocolectomy and continent ileostomy (Lal and Gallinger 2000).

Microsatellite Instability Pathway

In contrast to the CIN pathway, there is a distinct group of CRCs that does not show large chromosomal abnormalities. These diploid tumors have a different type of genetic instability in which the abnormalities lie at the nucleotide level. The propensity for deletion or gain of short DNA sequences in these tumors has been termed microsatellite instability (MSI).

Changes in Microsatellites Can Alter Downstream Genes

Microsatellites are short sequences in genomic DNA that comprise repetition of one to four nucleotides. These mono/di/tri or tetranucleotides can be repeated ten to hundreds of times in the sequence. The most common microsatellite in humans is the repetition of cytosine-adenine dinucleotide (CACACACA … or $[CA]_n$). Due to the repetitive nature of these sequences, they are prone to errors during DNA replication. Under normal conditions, these mistakes are corrected by highly conserved DNA repair mechanisms during cell replication. However, if the repair process is defective (such as in Lynch syndrome), microsatellite sequences can be altered, leading to microsatellite instability (MSI). A change in the length of a microsatellite can lead to a frameshift mutation in genes downstream to the microsatellite sequence, which shifts the reading frame of RNA polymerase, with the end result being a change in the amino acid sequence of the gene product.

Thibodeau and colleagues identified a subset of CRCs with highly variable microsatellites, and identified that 89% of these MSI tumors were in the proximal colon and that patients with MSI CRCs had a better prognosis (Thibodeau et al. 1993). Therefore, they hypothesized that the MSI pathway could represent an alternative pathway to CRC formation.

Lynch Syndrome

It became clear in the mid-1990s that Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC) and originally described by Warthin in 1913 and further characterized by Lynch in the mid-1960s, is associated with MSI (Lynch and Lynch 1985; Peltomäki et al. 1993). Lynch syndrome is responsible for up to 2–6% of CRCs (Aaltonen et al. 1998; Lamberti et al. 2006). The syndrome is characterized by increased risk of carcinogenesis in the gastrointestinal tract, endometrium, and ovary, and rarely in the urogenital tract, hepatobiliary tract, and pancreas (Aarnio et al. 1999). The lifetime 5–6% risk of developing CRC that is seen in the normal population is increased to 70–80% in Lynch syndrome (Aarnio et al. 1999; Chung and Rustgi 2003). As a result of this, regular colonoscopic surveillance is recommended and has been shown to reduce CRC-related mortality from 22% to 8%

(Monahan et al. 2020). The CAPP2 randomized control trial has shown that chemoprophylaxis with aspirin can reduce the risk of CRC formation in this group of patients (hazard ratio 0.41, 95% confidence interval 0.19–0.86, p 0.02) (Burn et al. 2011).

Just like FAP, Lynch syndrome has an autosomal dominant inheritance. The underlying cause is usually a germline mutation in one of the DNA mismatch repair genes. The most commonly mutated genes are human MutL homologue 1 (*MLH1*) found on chromosome 3p and human MutS homologue 2 (*MSH2*) located on chromosome *2p*. Other less commonly involved genes in Lynch syndrome are human MutS homologue (*MSH6*), and human postmeiotic segregation increased 2 (*PMS2*) and 1 (*PMS1*). Tumors which are deficient in these mismatch repair mechanisms (MMR-d) have high levels of MSI (MSI-H) and show loss of the corresponding DNA mismatch repair protein by immunohistochemistry (Valle et al. 2019). Deletions affecting the polyadenylation site located in exon 9 of the Epithelial Cell Adhesion Molecule (*EPCAM*) gene located upstream of *MSH2* are associated with 2–3% of Lynch syndrome cases (Huth et al. 2012). Deletions in *EPCAM* lead to a transcriptional read-through, best regarded as epigenetic silencing of *MSH2*.

Unlike polyposis syndromes, Lynch syndrome usually presents with sparse colorectal tumors which cannot usually be distinguished clinically from sporadic tumors. Therefore, clinical criteria have been defined to identify these patients and those at risk. The Amsterdam and Bethesda Criteria (Table 1) help identify patients based on family history and the characteristics of the index tumor (Umar et al. 2004; Vasen et al. 1999).

Further testing for mutations in microsatellites is recommended in those individuals who fulfill any of the Bethesda criteria (Burt and Neklason 2005; Kaz and Brentnall 2006).

Two methods are available to detect dMMR/MSI phenotype: (i) expression of MMR proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) in tumor tissue by immunohistochemistry (IHC) and (ii) DNA MSI testing by PCR fragment analysis (Figure 5). MMR immunohistochemistry presents a sensitivity between 85% and 98% and specificity between 85% and 100% whereas the sensitivity of MSI testing by PCR ranges between 67% and 100%, with a specificity between 61% and 98% depending on the panel used (Guyot D'Asnières De Salins et al. 2021; Snowsill et al. 2017). The terminology used in MMR immunohistochemistry can be confusing as a pathological finding implies a loss of the normal nuclear staining, in which the tumor should be referred to as MMR deficient. The terminology negative and positive may be misleading and should be avoided.

The PCR-based method demonstrates increased sensitivity and accuracy when tumor tissue and germline DNA (the latter can be extracted from adjacent normal tissue) are processed separately and then compared. Tumors that show instability in at least 30% of the examined microsatellites are termed microsatellite instability high (MSI-H), those with less than 30% are microsatellite instability low (MSI-L), and those with no mutation are microsatellite stable (MSS) tumors (C. R. Boland et al. 1998). Since usually five microsatellites are used for testing, in practice this means that a tumor is called MSI-H if at least two out of five microsatellites are unstable. Traditionally, two PCR fragment analysis-based DNA microsatellite analysis panels have been established: the Bethesda

Table 1 Amsterdam and Bethesda criteria for the identification of patients with Lynch syndrome.

Amsterdam II criteria (1999)

All criteria must be met:

- Three or more relatives with histologically confirmed colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis, one affected relative being a first-degree relative of the other two; FAP should be excluded.
- Two or more successive generations are affected.
- At least one relative was diagnosed before the age of 50 years.

Revised Bethesda guidelines (2004)

One or more of the following criteria must be met:

- Colorectal cancer before the age of 50 years
- Synchronous or metachronous colorectal cancer or other Lynch syndrome-related tumors,[1] regardless of age.
- Colorectal cancer with MSI-H morphology[2] before the age of 60 years.
- Colorectal cancer (regardless of age) and a first-degree relative with colorectal cancer or a Lynch syndrome-related tumor before the age of 50 years.
- Colorectal cancer (regardless of age) and two or more first- or second-degree relatives diagnosed with colorectal cancer or an Lynch syndrome-related tumor (regardless of age).

[1] Lynch syndrome-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma) tumors, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.

[2] Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring cell differentiation or medullary growth pattern.

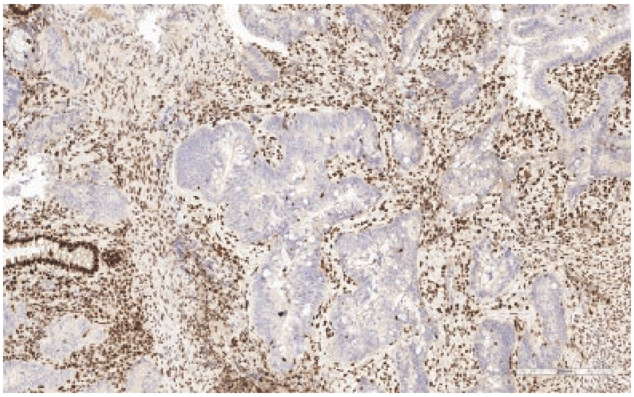

Figure 5 Example of a colorectal adenocarcinoma with loss of expression of MLH1. The immunohistochemistry reaction shows negative neoplastic glands within a positive background stroma.

panel, which assesses DNA mismatches in two mononucleotide repeats (*BAT-25* and *BAT-26*) and three dinucleotide repeats (*D5S346*, *DS123* and *D17S250*), and the modified MSI panel which assesses five mononucleotide repeats (*BAT-25*, *BAT-26*, *NR-21*, *NR-24*, and *MONO-27*). Both panels show overlapping performance in terms of MSI-H calling (Murphy et al. 2006). The sensitivity of the PCR-based diagnosis increases when the percentage of tumor cells in the tissue analyzed exceeds 30%.

Progress in technology and in particular the use of large targeted next generation sequencing (NGS) panels now allows the establishment of the diagnosis of MSI-H cancer (NGS-MSI). This methodology has shown high diagnostic concordance with traditional PCR fragment analysis (Vanderwalde et al. 2018).

It is worth noting that MSI can be also seen in about 15% of sporadic CRCs, and therefore an MSI-H tumor itself is not diagnostic for Lynch syndrome.

Hereditary CRC with MMR/MSI Discrepancy

About half of CRC families that meet the Amsterdam criteria have no identifiable germline mutations in the MMR genes. These families also have a lower lifetime CRC risk than families with Lynch syndrome and there is no increased risk of extracolonic tumors (Lindor et al. 2005). Analysis of these MMR-proficient tumors has failed to identify other genes that could explain these inherited forms of CRC, with the only candidate gene that has shown an association being *RPS20* (*ribosomal protein S20*) (Nieminen et al. 2014). In addition to this, rare germline *MLH1* promoter hypermethylation has been identified as a potential cause (Hitchins et al. 2005).

Sporadic MSI-Associated Colorectal Cancer

The vast majority of CRCs are sporadic, and most of these follow the conventional/chromosomal instability pathway. However, as mentioned before, about 15% of sporadic CRCs are associated with deficiency in the DNA mismatch repair machinery leading to DNA microsatellite instability. In contrast to Lynch syndrome, which relates to germline pathogenic variants in the genes encoding DNA mismatch repair proteins, these tumors show sporadic somatic inactivation of MMR genes. In the vast majority of cases, MSI in sporadic CRCs relates to epigenetic downregulation of MLH1. These epigenetic changes usually involve the methylation of cytosine residues in cytosine and guanine-rich regions (called CpG islands) in promoter sequences of the genes involved. As a consequence, there is no transcription of the gene. The majority (approximately 80%) of sporadic dMMR cases are caused by methylation of the *MLH1* gene promoter, whereas more than 70% of hereditary cases are associated with germline mutations in the *MLH1* and *MSH2* genes (Koopman et al. 2009; Latham et al. 2019).

Classification of sporadic CRCs based on microsatellite instability has profound clinical implications. MSI-H CRCs have consistently been shown to have a better prognosis compared to those with intact mismatch repair mechanisms. A systematic review of 32 studies comprising a total of 7,642 cases showed a combined hazard ratio for overall survival of 0.65 (95% confidence interval 0.59 to 0.71) for MSI-H compared to MSS CRCs (S Popat et al. 2005). One of the potential mechanisms for this appears to be the higher expression of neo tumor-specific peptides in MSI-H tumors (Linnebacher et al. 2001). These neoantigens are displayed by the major histocompatibility complex (MHC) on the surface of tumor cells, which in turn triggers a T-cell mediated cytotoxic anti-tumor immune response (Schumacher and Schreiber 2015). As well as its use in prognostication, MSI status impacts treatment strategy. For example, Jover and colleagues demonstrated that dMMR tumors do not respond to 5-fluorouracil based chemotherapy (Jover et al. 2009). Likewise, the immune checkpoint inhibitors nivolumab and pembrolizumab which block the programmed death (PD-1) receptor have been approved for the treatment of colorectal cancer with MSI-H or deficient MMR status (Le et al. 2015; Overman et al. 2017).

Serrated Neoplasia Pathway

More recently, a serrated neoplasia pathway to colorectal carcinogenesis has been described. The precursor lesion in this pathway is the serrated polyp. Although they represent a heterogeneous group, the characteristic feature of serrated polyps is the saw-toothed infolding of the crypt epithelium (Leggett

Table 2 Histological features of serrated lesions/polyps.

Hyperplastic polyps • Goblet cell-rich type (GCHP) • Microvesicular type (MVHP)	Small polyps in distal bowel with normal architecture and proliferation. GCHP has mature goblet cells in the upper crypt and harbor *KRAS* mutations in 50%. MVHP have enlarged micro-vacuolated columnar cells in upper crypt and harbor *BRAF* mutations in 70–80%.
Sessile serrated lesions (SSL)	Different from hyperplastic polyps, SSLs show abnormal architectural features such as branching of crypts, dilation of crypt base and growth of crypts parallel to muscularis mucosa. *BRAF* mutations are detected in up to 90% of SSLs. Low grade dysplasia relates to a loss of mismatch repair protein function and can be detected immunohistochemically.
Traditional serrated adenoma (TSA)	Characterized by overall protuberant growth pattern with villiform projections, characteristic ectopic crypt foci that develop orthogonally to the crypt axis and tall columnar cells with pencillate nuclei and eosinophilic cytoplasm.
Mixed serrated polyp	Contains components from the above categories.

and Whitehall 2010). A classification system was proposed by Snover and colleagues, shown in Table 2 (Snover et al. 2005).

While sporadic hyperplastic polyps are common and benign, sessile serrated polyposis (SSP) is a rare condition characterized by multiple serrated polyps, some of which can be >1cm in diameter (Winawer et al. 1997). Several studies have confirmed an increased risk of CRC in patients with SSP (35–50%), suggesting that serrated lesions have pre-malignant potential (Chow et al. 2006; Hyman et al. 2004).

Clinical criteria were proposed by the World Health Organisation in 2019 for the diagnosis of serrated polyposis. These are in Table 3:

Table 3 WHO criteria for the diagnosis of sessile serrated polyposis.

Criterion 1: > 5 serrated lesions proximal to the rectum, all being ≥ 5 mm in size, with ≥ 2 being 10 mm in size

Criterion 2: > 20 serrated lesions of any size distributed throughout the large bowel, with ≥ 5 being proximal to the rectum

Note that any histological subtype of serrated lesion is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies.

Additionally, sessile serrated lesions (SSLs) have been shown to be precursors to tumors with MSI (C. Richard Boland and Goel 2010). In the sporadic setting, conventional adenomas rarely show MSI whereas serrated polyps sometimes have MSI and loss of MLH1 expression (Iino et al. 1999).

Toyota and colleagues identified a subset of sporadic CRCs that showed high levels of CpG island methylation (both in *MLH1* and in other cancer-specific genes), a group called CpG island methylator phenotype (CIMP +) (Toyota et al. 1999). Yang and colleagues detected CIMP, in increasing order of frequency, in MVHP (47%), SSL (75%) and TSA (80%), indicating the sequence of events in the progression from precursor to dysplastic lesion (Yang et al. 2004). As well as being present in serrated polyps, CIMP has been identified in histologically normal mucosal biopsies, supporting the importance of a colorectal field in the development of serrated neoplasia (Worthley et al. 2010).

In addition to CIMP, *BRAF* mutations have been implicated in the vast majority of sessile serrated adenomas but almost never in conventional adenomas (Kambara et al. 2004). *BRAF* mutations are not prevalent in Lynch syndrome, strengthening its association with the serrated pathway rather than MSI (Yang et al. 2004). An activating mutation in *BRAF* (typically *V600E*) leads to constitutive activation of the mitogen-activated protein kinase pathway, leading to cell proliferation and survival independent of EGFR activation. *BRAF* appears to be mutated early in the serrated pathway as 70–76% of MVHP are *BRAF*-mutant, and *BRAF* mutations are found in aberrant crypt foci, which are the earliest histologically evident lesions in the serrated pathway (O'Brien et al. 2006; Rosenberg et al. 2007). More recently, a role for mutations in *RNF43* in the serrated pathway has been proposed. Yan and colleagues found that 85% of MSI-H tumors with MLH1 promoter methylation had a mutation in *RNF43*, compared to only 33% of tumors without *MLH1* promoter methylation (Yan et al. 2017).

Rarer Inherited Colorectal Cancer Syndromes

With the widespread use of NGS on colorectal tumors, more pathogenic variants are being associated with susceptibility to

Table 4 Summary of rare inherited colorectal cancer predisposition syndromes.

	Syndrome	Genetic defect	Features
Polyposis	MUTYH (or MYH)-associated polyposis (MAP)	MYH	<100 colorectal adenomas by the third decade of life.
	Polymerase proofreading-associated polyposis (PPAP)	POLE, POLD1	Multiple colorectal adenomas. Increased risk of endometrial, brain, breast, ovarian, and pancreatic cancers.
Hamartomatous	Peutz-Jehgers Syndrome (PJS)	LKB1 (also called STK11)	GI hamartomatous polyps, mucocutaneous pigmentation. Increased risk of pancreatic, stomach, breast, ovarian, lung, and endometrial cancer.
	Juvenile Polyposis Syndrome (JPS)	SMAD4, BMPR1A	Mucocutaneous telangiectasias, congenital cardiopulmonary defects. Increased risk of pancreas, stomach, and small bowel cancers.
	Cowden disease	PTEN	Macrocephaly, oral, and skin papillomas. Increased risk of breast and thyroid cancers.

CRC. While these contribute very little to the worldwide burden of CRC, these syndromes help shed more light on the molecular mechanisms that underpin colorectal tumorigenesis. These syndromes, summarized in Table 4, are broadly classified as polyposis (including FAP or attenuated FAP, as discussed before), non-polyposis (Lynch syndrome) and hamartomatous syndromes.

Colitis Associated Cancer

An alternative route for CRC development relies on the presence of chronic inflammation. Indeed, a wealth of evidence has demonstrated that the prevalence of CRC in patients with inflammatory bowel disease (IBD) (ulcerative colitis or Crohn's disease) is significantly increased relative to the healthy population (Ekbom et al. 1990; Winther et al. 2004). In addition to long disease duration, the severity of inflammation is a risk factor for the development of CRC in inflammatory bowel disease (Gillen et al. 1994).

The underlying mechanism that promotes tumorigenesis in the context of chronic inflammation remains to be elucidated but is likely to be multifactorial. Pro-inflammatory pathways such as the NF-kB, IL-6/STAT3, COX2/PGE2 and IL-23/Th17 are likely to be involved by regulating the expression of certain inflammatory mediators and promoting a tumor-supporting environment (O'Connor et al. 2010). In contrast to sporadic CRC, the sequence of events in colitis-associated CRC appears to be different. In particular, *TP53* mutations (Figure 6) appear to be an early event as they are detected not only in precancerous lesions, but also in non-neoplastic mucosa in the context of chronic inflammation (Galandiuk et al. 2012; Yin et al. 1993). Furthermore, *APC* and *KRAS* mutations are less prevalent in colitis-associated CRC, arguing the case for the selection of certain cancer-associated mutations by chronic inflammation (Burmer et al. 1990; Tannin et al. 1995).

Endoscopic surveillance in patients with IBD is crucial and has been shown to reduce the incidence of colitis-associated colorectal cancer (Castaño-Milla et al. 2014). In the UK, the British Society of Gastroenterology (BSG) and Association of Coloproctology for Great Britain and Ireland (ACPGBI) have issued guidelines for CRC screening in patients with IBD (Table 5) (Cairns et al. 2010; Lamb et al. 2019). All patients with ulcerative colitis or Crohn's colitis are recommended to have a screening colonoscopy approximately 10 years after the onset of colitic symptoms. The frequency of subsequent colonoscopic surveillance is then determined by stratifying patients into low,

Table 5 Summary of BSG/ACPGBI guidelines for colonoscopic surveillance for CRC in IBD.

Low risk (offer colonoscopy at five years)

- Extensive but quiescent ulcerative colitis or
- Extensive but quiescent Crohn's disease or
- Left-sided ulcerative colitis (but not proctitis alone) or Crohn's colitis of a similar extent.

Intermediate risk (offer colonoscopy at three years)

- Extensive ulcerative or Crohn's colitis with mild active inflammation that has been confirmed endoscopically or histologically or
- Post-inflammatory polyps or
- Family history of colorectal cancer in a first-degree relative aged 50 years or over.

High risk (offer colonoscopy at one year)

- Extensive ulcerative or Crohn's colitis with moderate or severe active inflammation that has been confirmed endoscopically or histologically or
- Primary sclerosing cholangitis (including after liver transplant) or
- Colonic stricture in the past five years or
- Any grade of dysplasia in the past five years or
- Family history of colorectal cancer in a first-degree relative aged under 50 years.

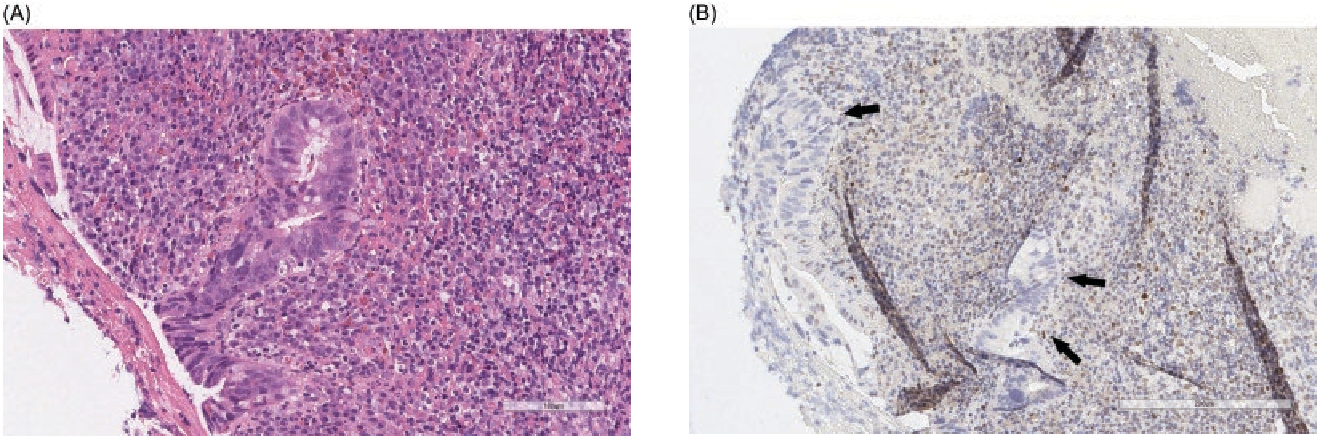

Figure 6 Case of inflammatory bowel disease with high grade dysplasia characterized by nuclear atypia and loss of maturation in crypt epithelium (A). The same crypt is seen in panel B (arrow) showing abnormal loss of TP53 expression contrasting with positive nuclei in the background inflammatory cell infiltrate.

intermediate and high-risk groups based on their disease burden, family history of CRC, presence of primary sclerosing cholangitis and endoscopic appearance at the index colonoscopy.

Transcriptomic Classification of Colorectal Cancer

The heterogeneous nature of CRC has meant that stratification of patients into clinically actionable groups has been difficult. In an effort to integrate molecular characteristics into classification, the consensus molecular subtypes (CMS) were introduced in 2015 (Guinney et al. 2015). By making use of differences in tumor biology rather than clinical outcomes, the CMS classification attempted to capture the intrinsic molecular heterogeneity of CRC.

Four subtypes were identified (CMS1-4) based on differential gene expression of the tumor tissue (comprising both the epithelium and stroma). CMS1 is enriched for MSI tumors and *BRAF* mutations, and displays high immunogenicity. CMS2 tumors have marked Wnt and Myc activation, and these tumors display high levels of chromosomal instability. CMS3 tumors are enriched for *KRAS* mutations and have features of metabolic dysregulation. CMS4 tumors on the other hand are mesenchymal and show activation of the TGFB pathway, with stromal invasion, angiogenesis and an immunosuppressive phenotype (Becht et al. 2016).

The CMS classification has been shown to be of prognostic significance. Primary CMS4 tumors have been associated with worse overall survival compared with CMS1 and CMS2 cancers (ten Hoorn et al. 2021). Similarly, adjuvant chemotherapy has been shown to be more effective in CMS2 and CMS3 tumors. However, a criticism of the CMS classification has been that it allocates a significant weight to the stromal content of the tumor, thereby masking low abundance epithelial transcripts. The five CRC intrinsic subtypes (CRIS) have been developed to address this (Isella et al. 2017). Increasingly, molecular profiling and patient classification into molecular subtypes are being used for treatment allocation in oncological trials. It remains to be shown whether this approach will increase the treatment effect by reducing the number of patients who do not respond to treatment.

Histopathology

Careful and accurate pathology reporting of CRC is vital because pathology reports are used not only to confirm the diagnosis, but also to provide prognostic and predictive information allowing clinicians to deliver a high standard of care for patients and appropriate management for specific clinical circumstances. The report also provides valuable audit data on the accuracy of other clinical services such as radiology, surgery, oncology and screening programs. Systematic review of all original colorectal pathology reports, macroscopic images/descriptions and slides also acts to audit the quality and consistency of reporting within the pathology department and to collect accurate data for cancer registration and epidemiology, facilitate high quality research, provide education, and plan service delivery (Loughrey et al. 2018). Pathologists are therefore well placed to help establish and maintain high standards of clinical care for patients with CRC as part of a multidisciplinary team.

The specimens examined by the pathologists will be considered separately, starting from the initial assessment of diagnostic biopsies and progressing through local excisions to resections. This approach broadly corresponds to the order in which surgical specimens are examined as patients' progress along the colorectal cancer pathway.

Biopsy Diagnosis of Large Bowel Adenocarcinoma

Frequently, the pathologist is required to interpret biopsies taken from polypoid, ulcerated or flat lesions which are endoscopically suspicious of malignancy. The aim is to confirm the diagnosis of malignancy, classify the type of malignancy (including primary versus secondary) and assess tumor grade. Less frequently, biopsies taken from sites other than the colon and rectum may contain deposits of colorectal adenocarcinoma. In such cases, the pathologist is strongly aided by detailed clinical information, including appropriate radiologic imaging and may require the use of immunohistochemical stains. Depending on the biopsy appearance, a report of metastatic adenocarcinoma may be suggestive of primary colorectal malignancy.

Endoscopic biopsy confirmation of colorectal adenocarcinoma depends upon the identification of unequivocal evidence of invasion by tumor cells through the muscularis mucosae into the submucosa. A desmoplastic stromal reaction may provide a clue to the diagnosis. Biopsies entirely composed of superficial fragments of "dysplastic" epithelium with no relation to muscularis mucosae or containing only necrotic tissue are deemed inadequate and the pathologist is unable to independently verify the diagnosis of malignancy. Small biopsies from invasive tumors may also fail to accurately represent the true tumor grade, while areas of ulceration and associated inflammation from superficial parts of the tumor may lead to the mistaken interpretation of a poorly differentiated tumor.

It has been widely recommended that all CRCs should be tested for MMR status with the purpose of detecting Lynch syndrome at the time of diagnosis. As will be discussed in more detail further on in this chapter, it is also important for clinical management and prognosis. The initial test can be MSI or MMR immunohistochemistry, depending on local circumstances. The recommendation is that MMR immunohistochemistry should be performed on the endoscopic biopsy, assuming this contains diagnostic material, and the main reasons for this are:

- better fixation facilitates interpretation.
- the result is available clinically in a more timely fashion, which is essential in the neoadjuvant pathway.
- avoids radiotherapy-induced artefacts that can affect interpretation.
- patients who do not undergo surgery are tested.

Endoscopists should be encouraged to take more and larger biopsy samples from all tumors, to allow confident diagnosis and provide adequate tumor tissue for any required downstream testing for example, for Lynch syndrome (Loughrey et al. 2018).

Local Excision Specimens

A biopsy diagnosis of adenocarcinoma may be followed by planned local excision, which may be undertaken as a curative procedure for some patients with early rectal cancer or as a palliative procedure in patients unsuitable for resectional surgery. Lesions may be removed by endoscopically (endoscopic mucosal resection or endoscopic submucosal dissection) or, in the case of some rectal tumors, via transanal minimally invasive surgery.

As the majority of large bowel adenocarcinomas arise from pre-existing adenomas and sessile serrated lesions, screening colonoscopy and therapeutic polypectomy has a potential to reduce CRC burden by early detection and removal of benign polyps, thus decreasing CRC incidence and mortality (Lin et al. 2021). Careful assessment and reporting of these premalignant lesions requires a standardized approach and the use of consistent terminology amongst pathologists, gastroenterologists, and colorectal surgeons.

Conventional colorectal adenomas are subtyped according to their histological pattern. Tubular adenomas, which are the most common subtype, show normal crypt architecture (Figure 7) whereas villous adenomas are composed mainly of leaf- or finger-like projections. Tubulovillous adenomas show a mixture of both patterns (Figure 8). The grading of the dysplasia is based mainly on the degree of architectural complexity

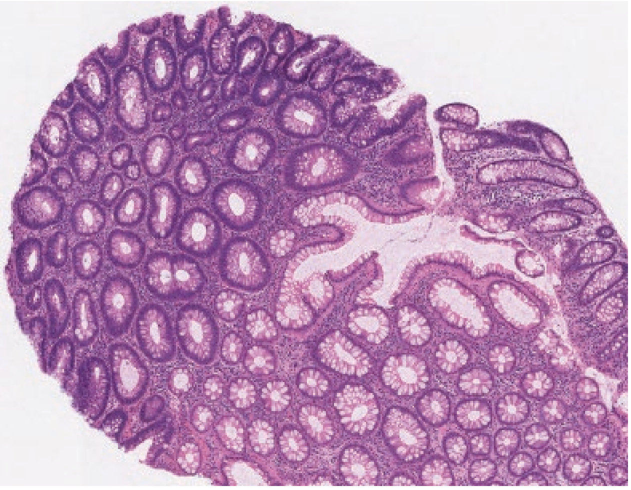

Figure 7 Tubular adenoma (left) showing similar architecture as adjacent non-dysplastic mucosa (right).

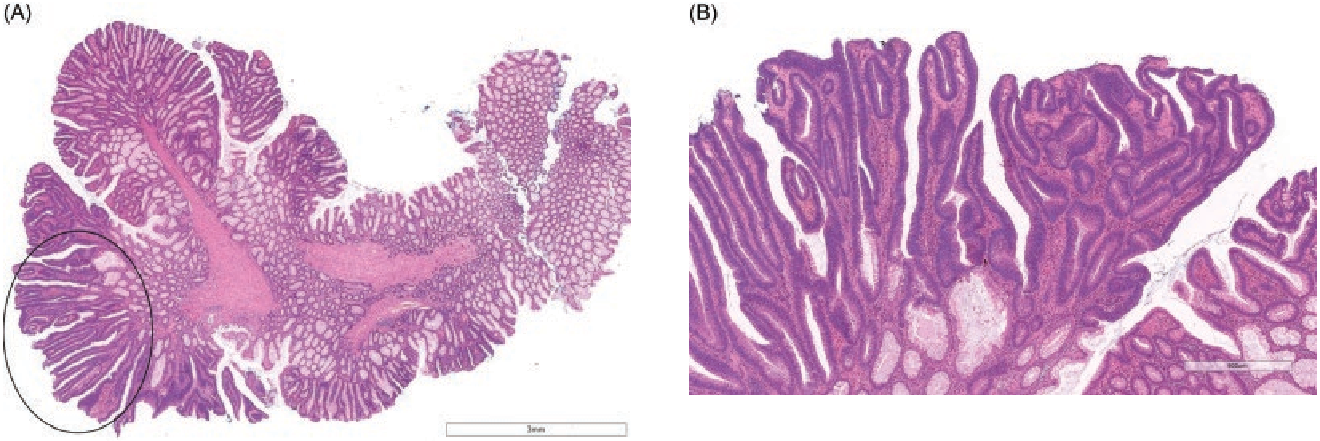

Figure 8 Tubulovillous adenoma (A). Figure (B) is a higher magnification of the encircled area showing villiform projections.

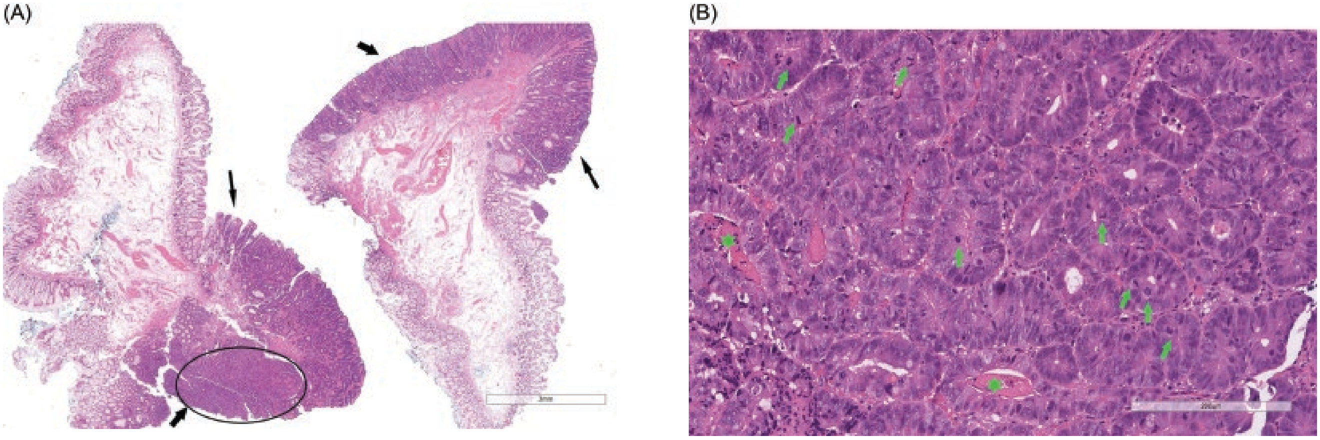

Figure 9 Tubular adenoma with low grade dysplasia (A, thin arrow) and high-grade dysplasia (A, thick arrow). Encircled area (B) shows nuclear crowding with reduced stroma between glands, nuclear crowing, frequent mitotic figures (green arrows) and intraluminal necrosis (green star).

supplemented by cytological atypia. The use of a two-tier stratification of the adenomatous dysplasia into low grade and high grade is recommended as this provides a uniform system for integrating global histopathology grading data (Figure 9). Although used in the Japanese literature, in order to avoid overtreatment of lesions considered to have negligible risk of metastatic spread, the terms carcinoma in situ and intramucosal carcinoma are not used in Europe and the USA.

The term "advanced adenoma" encompasses a group of adenomas larger than 10 mm, tubulovillous or villous architecture, and/or high-grade dysplasia. These are associated with a high risk of synchronous or metachronous adenomas, the former indicating the need for a full colonoscopy and the latter more stringent surveillance (WHO 2019).

As mentioned before, serrated lesions (SLs) and polyps are characterized by a sawtooth or stellate architecture of the epithelium. They are named according to their morphological appearance as hyperplastic polyp (HP) (Figure 10), sessile serrated lesion (SSL), sessile serrated lesion with dysplasia, traditional serrated adenoma (TSA) and mixed lesions (Table 2) (Bateman and Shepherd 2015). The distribution of SLs varies with the type: HPs and TSAs are usually found in the left colon, while SSLs occur more often in the proximal colon (Carr et al. 2009; Lash et al. 2010; Qazi et al. 2014). SSLs are commonly 10 mm or more, particularly the ones with dysplasia, and show an overall distortion of the normal crypt architecture, probably resulting from alterations of the proliferative zone (Figure 11) (Yang et al. 2015). Tiny distal HPs do not appear to be associated with significant risk of CRC development, while larger lesions with features of SSLs can be associated with the development of dysplasia and adenocarcinoma (East et al. 2017). SSLs can show dysplasia that can be low or high grade in nature and it is believed that dysplastic lesions are associated with faster progression to

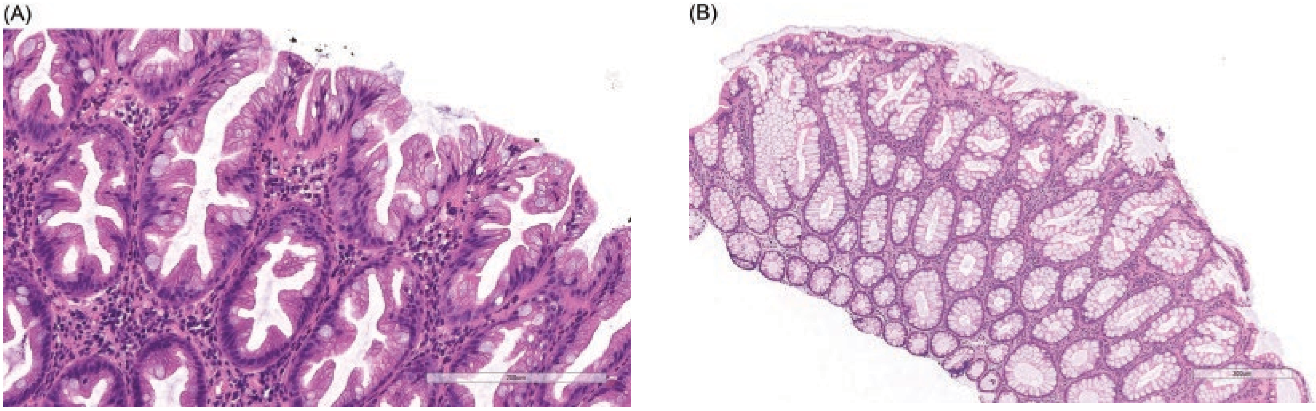

Figure 10 (A) Microvesicular hyperplastic polyp with serrated appearance of the crypts. (B) Goblet cell-rich hyperplastic polyp.

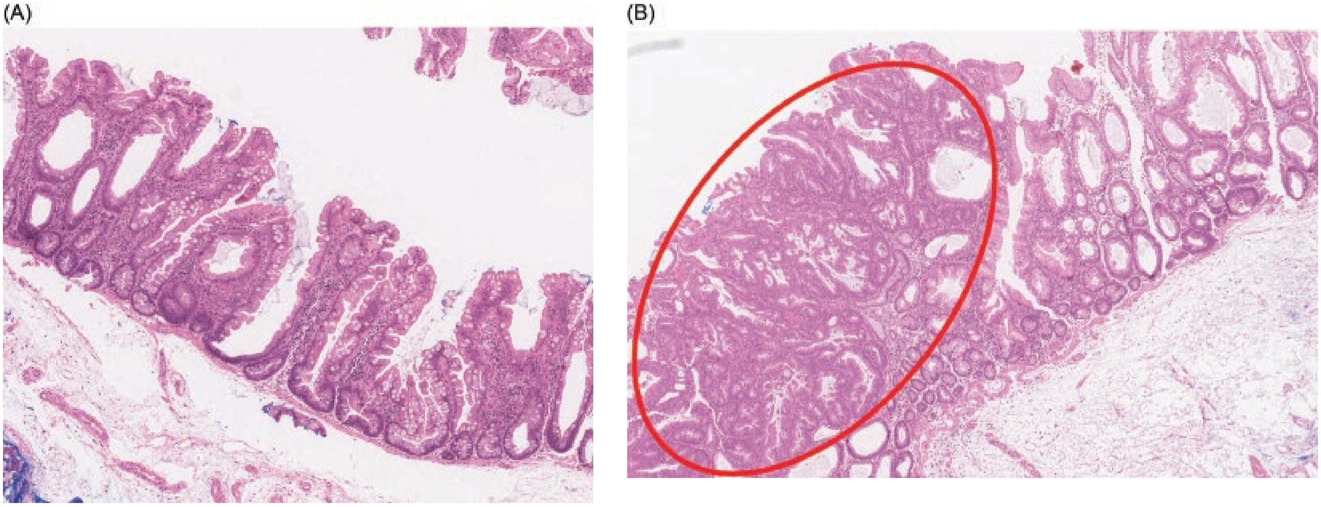

Figure 11 (A) Sessile serrated lesion with dilation extending to the base of crypts and crypt distortion. (B) Same lesion with an area of high-grade dysplasia.

adenocarcinoma than "classical" adenomas. TSAs can present as large polyps in the left colon and rectum or as flat lesions predominantly in the proximal colon. They are characterized by the presence of dysplasia, almost always show areas of conventional adenomas and seem to have a more rapid malignant potential.

The principles of reporting an adenocarcinoma that has developed within an adenomatous lesion and has been removed by local excision are the same as in major resections. However, a number of features require special attention in local excisions of (presumed) early cancers with curative intent because they are used to determine the necessity for more radical surgery. In addition to the assessment of completeness of excision, these include the recording of parameters that predict the presence of lymph node metastatic disease in early tumors, namely tumor size, poor differentiation, the depth of invasion into the submucosa, the presence of submucosal lymphatic or venous invasion and margin involvement (Beaton et al. 2013; Ueno et al. 2004).

Tumors that invade the muscularis propria usually require further surgery. For many years the Haggitt (1985) and Kikuchi (1995) classifications (Figure 12) have been used to sub-stage the colorectal adenocarcinomas in relation to depth of invasion into submucosa in pedunculated and sessile tumors respectively. Haggitt and colleagues found that "level 4" invasion, in which the tumor extended beyond the stalk of the polyp into the submucosa but did not invade the muscularis propria, was an adverse factor. Neither system is always easy to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue. The Kikuchi level system requires division of the submucosa into thirds and this is not possible to do accurately unless muscularis propria is included in the specimen.

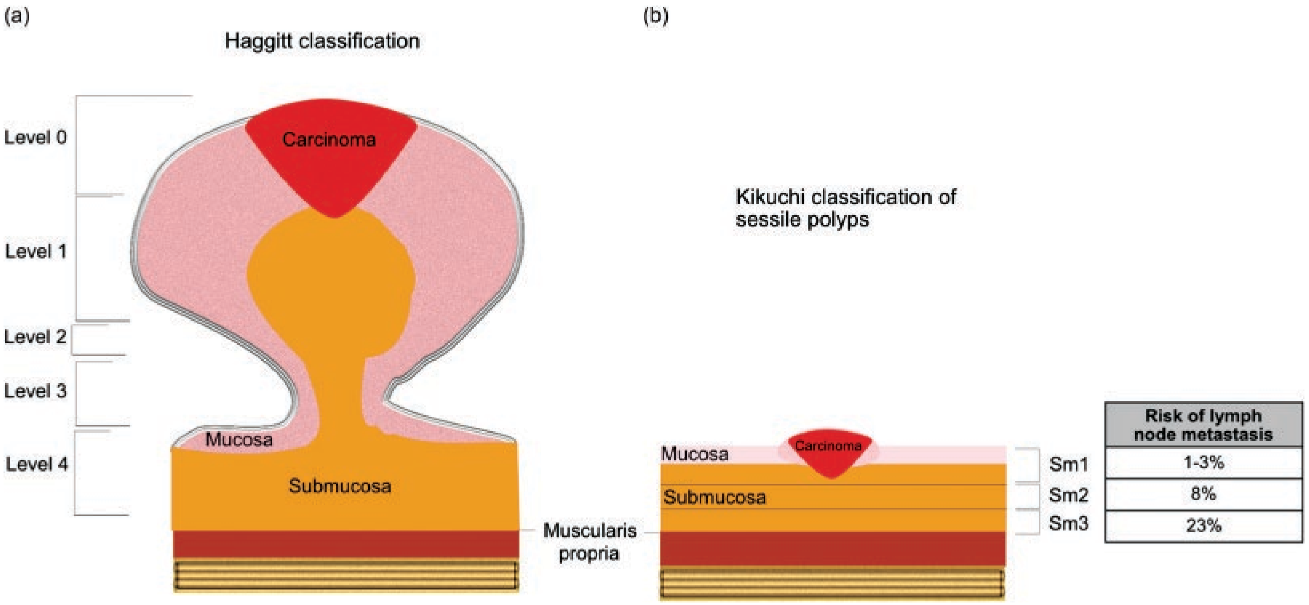

Figure 12 Substaging of T1 cancer. (a) Haggitt staging of pedunculated adenocarcinoma. (b) Kikuchi staging in sessile T1 adenocarcinoma.

More recently, Ueno et al. (2004) have proposed that the absolute thickness of the invasive tumor (depth of invasion beyond the muscularis mucosae) and the width of tumor invasion provide more objective measures of potential risk of lymph node metastatic disease. At the moment, a firm recommendation cannot be made based on current evidence for one method of assessing local invasion over another and whenever possible, all three approaches should be mentioned in the pathologist report to facilitate data collection for further research and for local multidisciplinary teams to select which they consider to be most appropriate to management decisions.

Intact polypectomy specimens require assessment of both the peripheral (mucosal) and deep margins. Involvement of a peripheral margin may indicate the need for repeat endoscopy and further local excision if feasible. Involvement of the deep resection margin by invasive tumor has traditionally been an indication for considering surgical intervention.

Another emerging feature, particularly for local excision specimens, is the presence of tumor budding (single tumor cells or cell clusters of up to four tumor cells). Until recently, however, the application of this biomarker in clinical practice was limited by the lack of a standardized assessment and reporting methodology. In the context of CRC, tumor budding can be assessed according to the method agreed at the International Tumor Budding Consensus Conference (ITBCC) in 2016. Using the ITBCC scoring system, tumor budding is an independent predictor of lymph node metastasis in patients with pT1 CRC and an adverse prognostic factor that should warrant consideration of adjuvant chemotherapy in patients with stage II colon cancer (Lugli et al. 2021). The most recent WHO classification of tumors (2019) has included this feature as an additional prognostic factor for CRC.

Tumor budding can not only be observed at the invasive tumor front (Figure 13), but also within the tumor bulk, referred to as intra-tumoral budding. Tumor budding can be observed in endoscopic biopsy specimens and their presence has been shown to be associated with advanced tumor stage assessed quantitatively (Lugli et al. 2021).

In an effort to combine the effect of depth of invasion with other prognostic factors, the ACPGBI issued a position statement in 2013, highlighting the role of the resection margin, degree of differentiation, tumor budding, lympho-vascular invasion, and mucinous differentiation in conferring a risk of residual disease following resection of a malignant polyp (Williams et al. 2013).

Resection Specimens

Colorectal resection specimens require careful handling and assessment if key prognostic data are to be determined reliably and accurately. The critical role of a skilled surgical technique and its effect on patient outcome (morbidity and mortality) is well established for anterior resection (AR) and abdomino-perineal excision of the rectum resection (APER) procedures in the treatment of rectal cancer. Audit of the adequacy of the surgical technique is regarded as a valuable source of feedback to colorectal surgeons, including an assessment of the resection margin (R) status.

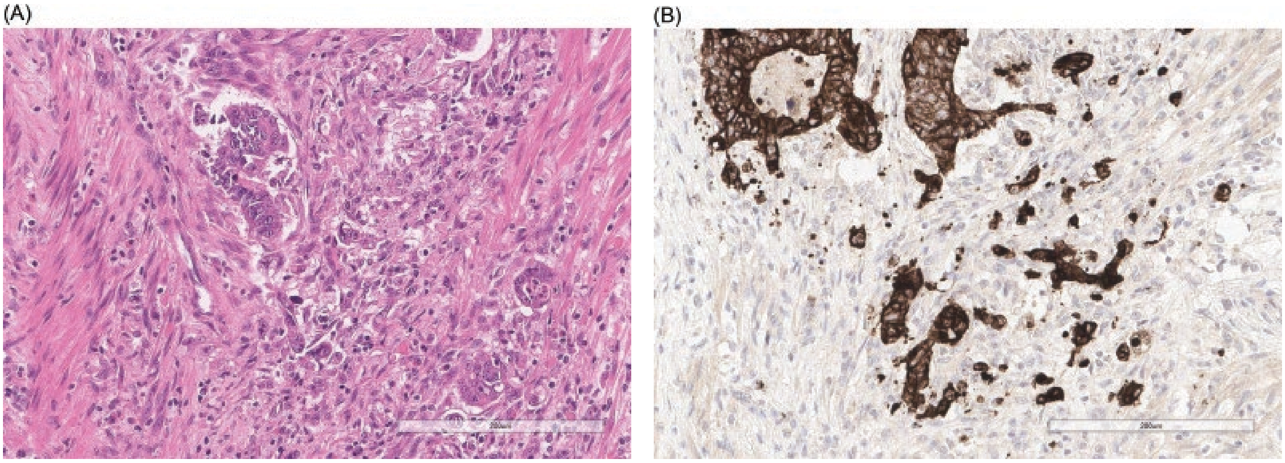

Figure 13 Tumor budding, single or small clusters of neoplastic cells infiltrating the desmoplastic stroma, seen on H&E (A) and highlighted with immunohistochemistry for Cytokeratin in (B).

Ideally, specimens should be received fresh and unopened as soon as possible after surgical resection. The colorectal specimen should be photographed and carefully examined. In rectal specimens, particular attention should be given to the macroscopic assessment of the mesorectum which should be intact, with no defect deeper than 5 mm and no coning toward the distal margin. A three-tier scoring system has been proposed: complete, which shows an intact mesorectum; nearly complete or intra-mesorectal; and incomplete when there is exposure of muscularis propria (Nagtegaal et al. 2002). This information predicts not only margin involvement but also local recurrence and survival. The plane of resection can also be used as a marker of the quality of surgery and continual feedback to multidisciplinary teams has led to improved quality of surgery and clinical outcomes with time (Nagtegaal et al. 2002; Quirke et al. 2009).

In addition to detailed macroscopic description which should mention tumor location and diameter, the pathology report should include information relating to the tumor type and differentiation; extent of local tumor invasion (pT stage) specifying if invasion in other organs or tumor perforation; resection margins; lymph node (LN) status (number present and number involved); presence of tumor deposits; intra and/or extramural venous invasion; lymphatic invasion and perineural invasion.

All of the lymph nodes that can be found in a specimen should be examined histologically as the number of lymph nodes identified in resection specimens from patients with stage II and stage III colon cancer has been positively correlated with survival (Chang et al. 2007). This positive correlation is supported by the results of a recent analysis by Lal et al. (2022) using cases from The Cancer Genome Atlas (TCGA) which shows that a high LN yield predicts overall and disease-free survival. In addition, they found no association of higher LN yield and increasing nodal positivity; and a high LN yield was strongly linked to an activated immune response in tumors. Their data suggest that LN yield may be driven by an enhanced immune response in the primary tumor making nodes easier to identify ex vivo rather than intrinsic surgical or pathologist-specific factors.

Additional prognostic factors are tumor budding, and the inflammatory infiltrate (Loughrey et al. 2018; Lugli et al. 2021). In relation to inflammatory infiltrate, the presence of intratumoral lymphocytes and Crohn-like reaction are associated with improved outcome (Rozek et al. 2016). Tumor deposits (satellites) are an established adverse prognostic factor in colorectal cancer (Nagtegaal et al. 2016) and according to TNM 8, they are defined as "discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary tumor and without histological evidence of residual lymph node or identifiable vascular or neural structures". In the absence of lymph node metastasis in regional lymph nodes, the presence of a satellite deposits changes the tumor status to pN1c.

Regular audit of resection specimen reports should ensure that all of the relevant data is consistently and accurately recorded.

Preoperative Chemoradiotherapy-Related Changes in Surgical Specimens

Following neoadjuvant chemoradiotherapy, rectal tumors may show evidence of extensive regression with widespread necrosis and stromal fibrosis. Alterations in the appearance of the advancing front of tumor cells and a reduced lymphocytic response is also frequently seen. In some circumstances the tumor may be entirely absent from the specimen despite extensive sampling. Alternatively, small foci of residual tumor cells may appear isolated within the rectal wall. Lymph nodes, critical for accurate pathologic staging, may be small, difficult to find and display features of necrosis.

Table 6 Most commonly used system for assessing tumor regression grade (TRG) (Adapted from Langer and Becker 2018).

Grade	Mandard	AJCC 2010
TRG 0	–	No residual tumor cells (complete response)
TRG 1	Absence of residual cancer cells	Single cells or small groups of cancer cells (near complete response)
TRG 2	Rare residual cancer cells scattered through the fibrosis	Residual cancer cell with desmosplastic response (partial response)
TRG 3	An increased in number of residual cells, but fibrosis still predominates	Minimal evidence of tumor response (poor or no response)
TRG 4	Residual cancer outgrowing fibrosis	
TRG 5	Absence of regressive changes	

The response of rectal cancers to preoperative chemoradiotherapy is highly variable ranging from complete pathological response to no detectable effects. There is evidence that patients with completely excised rectal carcinomas, who have received neoadjuvant treatment that has resulted in complete or marked regression, have a better prognosis than those without significant regression (Hermanek et al. 2013; Maas et al. 2010). In order to allow meaningful comparisons of resected rectal tumors and to establish the prognostic value of histologic chemoradiotherapeutic change, various classification systems to assess tumor regression grade (TRG) have been proposed (Table 6). Pathologists should be encouraged to document the TRG in all patients receiving neoadjuvant chemoradiotherapy.

The Emerging Role of Molecular Diagnostics in Colorectal Cancer

As outlined throughout this chapter, molecular tumor characterization has become an integral part of the multidisciplinary approach in the management of patients with CRC over the past decade. Molecular diagnostics is of dual significance. First, it allows accurate classification of the underlying pathology, which itself guides treatment options that are becoming increasingly personalized. Secondly, it may inform on the presence of underlying hereditary tumor syndromes as outlined above, guiding surveillance and screening of relevant family members. The technological progress in molecular tumor characterization and access to large panel sequencing provide information on prognostic tumor factors and lead to the identification of targetable pathways and allow patients to access clinical trials.

MSI and mutations in *BRAF* and *RAS* are established predictive biomarkers in CRC (WHO classification of tumors 2019) and can be tested either by immunohistochemistry (*MMR* and *BRAF*^{V600E}) or sequencing.

In the UK, NICE recommends algorithmic testing for Lynch syndrome (NICE 2017) (Figure 14). MSI CRCs should have *BRAF* mutation testing and/or *MLH1* promoter methylation testing to distinguish between sporadic dMMR cancers and Lynch syndrome. Absence of *BRAF*$^{\mathrm{V600E}}$ mutation and/or absent *MLH1* promoter hypermethylation should prompt a recommendation of referral to clinical genetics for appropriate counselling and screening of the relevant MMR genes, as should loss of PMS2, MSH2, and/or MSH6 immunohistochemical expression (Loughrey et al. 2022). *BRAF*-wildtype cases with MSI have a good prognosis, and regardless of *BRAF* status, dMMR tumors have a poorer response to 5-fluorouracil-based chemotherapy but respond to immune checkpoint blockade (Le et al. 2017). More recently, Cercek and colleagues described complete clinical responses in all cases (n = 12) of dMMR stage II or stage III locally advanced rectal cancer treated with dostarlimab, an anti-PD-1 monoclonal antibody, without the need for chemoradiotherapy or surgery (Cercek et al. 2022).

Mutations in *KRAS* and *NRAS* also have therapeutic significance. Testing for *KRAS* and *NRAS* mutations in codons 12, 13, 59, 61, 117, and 146 in CRC with metastatic disease is recommended as it correlates with resistance to anti-epidermal growth factor (anti-EGFR) therapy (such as cetuximab and panitumumab) (Van Cutsem E, Lenz HJ, Köhne et al. 2015). Early-stage clinical trials have shown promising results with the *KRAS*^{G12C} specific covalent inhibitor sotorasib in *KRAS*^{G12C} mutant CRCs (Canon et al. 2019).

It is likely that the presence of *BRAF*^{V600E} mutation also confers resistance to anti-EGFR therapy. However, this can be rescued through triplet therapy with BRAF (encorafenib), EGFR (cetuximab) and MEK (binimetinib) inhibitors, which have been shown to increase overall survival compared to standard treatment (Kopetz et al. 2019). Therefore, most modern guidelines also recommend testing metastatic CRC for BRAFV^{600E} mutation (Loughrey et al. 2022; Pietrantonio et al. 2015).

A number of studies investigating other possible biomarkers in colorectal cancer are underway and other tests will inevitably emerge in the near future. For example, HER2 activation (which leads to MAPK phosphorylation and subsequent resistance to EGFR inhibition) appears to be a possible druggable target, with combination therapy of trastuzumab plus lapatinib or trastuzumab and pertuzumab (Meric-Bernstam et al. 2019; Sartore-Bianchi et al. 2016). Table 7 summarizes current and emerging biomarkers and their clinical significance.

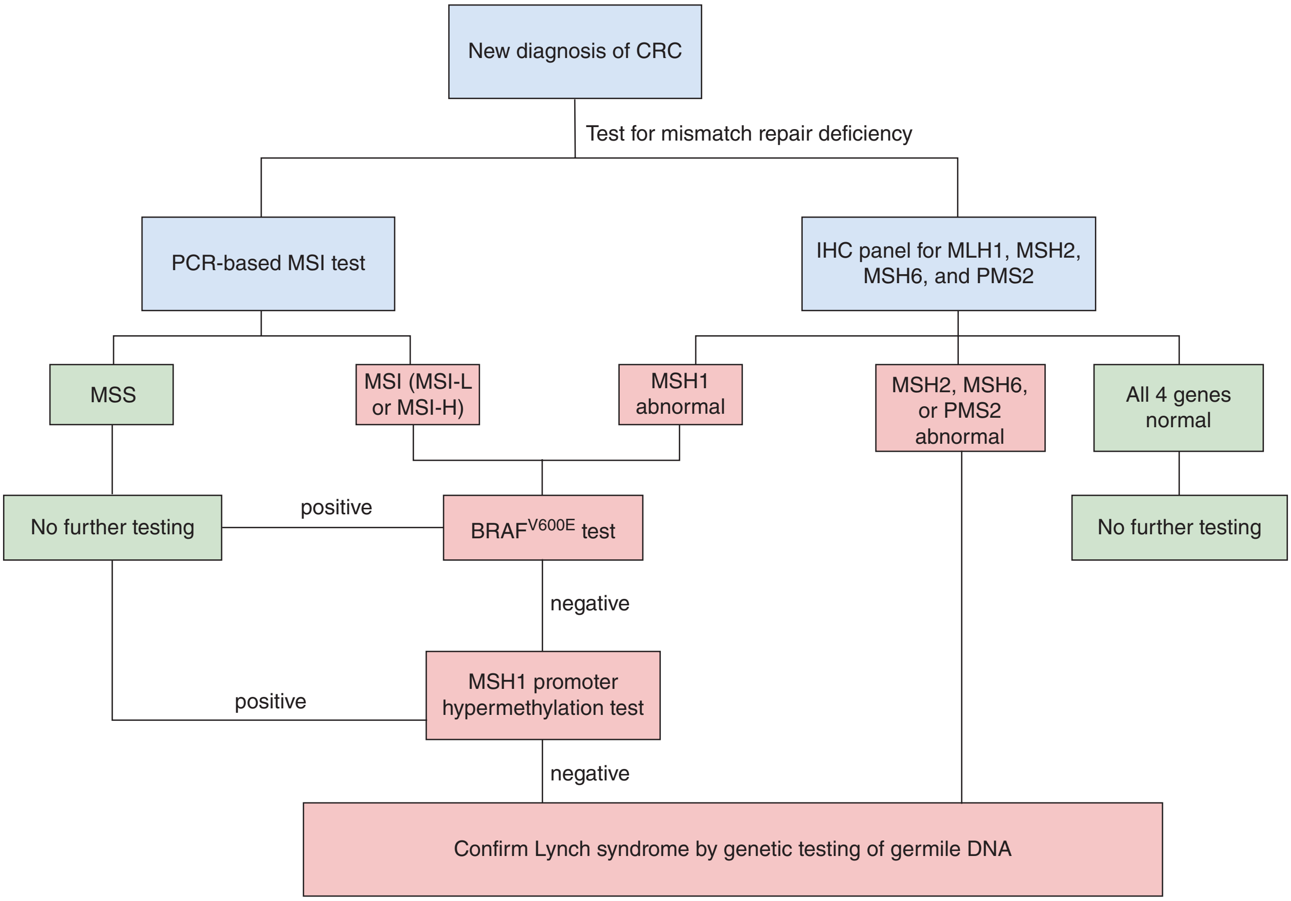
New diagnosis of CRC
Test for mismatch repair deficiency
PCR-based MSI test
IHC panel for MLH1, MSH2, MSH6, and PMS2
MSS
MSI (MSI-L or MSI-H)
MSH1 abnormal
MSH2, MSH6, or PMS2 abnormal
All 4 genes normal
No further testing
positive
BRAFV600E test
No further testing
negative
MSH1 promoter hypermethylation test
positive
negative
Confirm Lynch syndrome by genetic testing of germile DNA

Figure 14 Flowchart of molecular testing algorithm suggested by NICE.

Table 7 Suggested markers for routine testing and their possible significance (in addition to prognostication).

Marker	Test	Present and possible future significance
Microsatellite instability (MSI)	PCR	• PD1 blockade
Mismatch repair (MMR) status	IHC	• Screening for Lynch syndrome
	NGS	• PD1 blockade
KRAS, HRAS, NRAS	PCR	• Resistance to anti-EGFR therapy
	NGS	• KRAS-specific inhibitors
BRAF^{V600E}	IHC	• BRAF-specific inhibitors
	NGS	
PIK3CA*	NGS	• Aspirin as adjuvant therapy
HER2*	IHC	• HER2 blockade
	NGS	
NTRK fusion*	NGS	• TRK inhibition
MET amplification*	NGS	• Resistance to anti-EGFR therapy
Consensus molecular subtyping*	Transcriptional profiling	• Targeted cetuximab (in CMS2) or bevacizumab (in CMS1)

* emerging biomarkers with current limited evidence.

Key Take Home Messages

CRC is highly heterogeneous in its pathogenesis and histopathological features.

Establishment of screening programs has allowed earlier diagnosis and understanding of early steps of pathogenesis of CRC.

Accurate classification of CRC and molecular characterization allows the best treatment decisions to be made and is useful for prognostication.

Increasingly, molecular testing is being used to identify patients with actionable genetic defects.

Knowledge Gaps

What is the role of the tumor microenvironment and microbiome in CRC formation and progression?

What are the drivers of metastasis in CRC?

To what extent does intra-tumoral genetic and transcriptomic heterogeneity contribute to treatment resistance in metastatic CRC?

Are there biomarkers that can be used for early detection of pre-neoplastic lesions?

Are there other biomarkers that are more predictive of treatment response which can improve targeted neoadjuvant or adjuvant therapy?

Trusted Websites for Further Reading

- The Royal College of Pathologists, United Kingdom.

Links to up-to-date UK-based histology reporting guidelines.
https://www.rcpath.org/profession/guidelines.html

- Association for Molecular Pathology, USA.

Up-to-date American guidelines on the use of molecular biomarkers.
https://www.amp.org/clinical-practice/practice-guidelines/colorectal-biomarker-guideline

- National Institute for Health and Care Excellence (NICE), United Kingdom.

UK guidelines on management of local and metastatic colorectal cancer and evidence review of the use of molecular biomarkers for systemic anti-cancer therapy.
https://www.nice.org.uk/guidance/ng151

- British Society of Gastroenterology (BSG)

Joint guidelines for the management of hereditary colorectal cancer.

https://www.bsg.org.uk/clinical-resource/guidelines-for-the-management-of-hereditary-colorectal-cancer-from-the-bsg-acpgbi-ukcgg

References

Aaltonen, L.A., Salovaara, R., Kristo, P. et al. (1998). Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *New Engl J Med* 338 (21): 1481–1487. doi: 10.1056/NEJM199805213382101.

Aarnio, M., Sankila, R., Pukkala, E. et al. (1999). Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 81 (2): 214–218. doi: 10.1002/(sici)1097-0215(19990412)81:2<214::aid-ijc8>3.0.co;2-l.

Aberle, H., Bauer, A., Stappert, J. et al. (1997). β-catenin is a target for the ubiquitin–proteasome pathway. *EMBO J* 16 (13): 3797–3804. doi: 10.1093/emboj/16.13.3797.

Armaghany, T., Wilson, J.D., Chu, Q., and Mills, G. (2012). Genetic alterations in colorectal cancer. *Gastrointest Cancer Res: GCR* 5 (1): 19–27. doi: 10.1007/978-0-85729-984-0_2.

Arnold, M., Sierra, M.S., Laversanne, M. et al. (2017). Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 66 (4): 683–691. doi: 10.1136/gutjnl-2015-310912.

Barker, N., Ridgway, R.A., Van Es, J.H. et al. (2009). Crypt stem cells as the cells-of-origin of intestinal cancer. *Nature* 457 (7229): 608–611. doi: 10.1038/nature07602.

Bateman, A.C. and Shepherd, N.A. (2015). UK guidance for the pathological reporting of serrated lesions of the colorectum. *J Clin Pathol* 68: 585–591.

Beaton, C., Twine, C.P., Williams, G.L., and Radcliffe, A.G. (2013). Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. *Colorectal Dis* 15: 788–797.

Becht, E., De Reyniès, A., Giraldo, N.A. et al. (2016). Immune and stromal classification of Colorectal cancer is associated with molecular subtypes and relevant for precision immunotherapy. *Clin Cancer Res* 22 (16): 4057–4066. doi: 10.1158/1078-0432.CCR-15-2879.

Bisgaard, M.L., Fenger, K., Bülow, S. et al. (1994). Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat* 3 (2): 121–125. doi: 10.1002/humu.1380030206.

Boland, C.R., Thibodeau, S.N., Hamilton, S.R. et al. (1998). A national cancer institute workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 58 (22): 5248–5257. http://www.ncbi.nlm.nih.gov/pubmed/9823339.

Boland, C.R. and Goel, A. (2010). Microsatellite Instability in Colorectal Cancer. *Gastroenterology* 138 (6): 2073–2087.e3. doi: 10.1053/j.gastro.2009.12.064.

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 68 (6): 394–424. doi: 10.3322/caac.21492.

Bruens, L., Ellenbroek, S.I.J., Suijkerbuijk, S.J.E. et al. (2020). Calorie restriction increases the number of competing stem cells and decreases mutation retention in the intestine. *Cell Reports* 32 (3): 107937. doi: 10.1016/j.celrep.2020.107937.

Burmer, G.C., Levine, D.S., Kulander, B.G. et al. (1990). C-Ki-ras mutations in chronic ulcerative colitis and sporadic colon carcinoma. *Gastroenterology* 99 (2): 416–420. doi: 10.1016/0016-5085(90)91024-Z.

Burn, J., Gerdes, A.M., MacRae, F. et al. (2011). Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 378: 2081–2087.

Burt, R. and Neklason, D.W. (2005). Genetic testing for inherited colon cancer. *Gastroenterology* 128 (6): 1696–1716. doi: 10.1053/j.gastro.2005.03.036.

Cadigan, K.M. and Nusse, R. (1997). Wnt signaling: a common theme in animal development. *Genes Devel* 11 (24): 3286–3305. doi: 10.1101/gad.11.24.3286.

Cairns, S.R., Scholefield, J.H., Steele, R.J. et al. (2010). Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 59 (5): 666–689. doi: 10.1136/gut.2009.179804.

Canon, J., Rex, K., Saiki, A.Y. et al. (2019). The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumor immunity. *Nature* 575: 217–223. doi: 10.1038/s41586-019-1694-1.

Carr, N.J., Mahajan, H., Tan, K.L. et al. (2009). Serrated and non-serrated polyps of the colorectum: their prevalence in an unselected case series and correlation of BRAF mutation analysis with the diagnosis of sessile serrated adenoma. *J Clin Pathol* 62: 516–518.

Castaño-Milla, C., Chaparro, M., and Gisbert, J.P. (2014). Systematic review with meta-Analysis: the declining risk of colorectal cancer in ulcerative colitis. *Aliment Pharmacol Ther* 39 (7): 645–659. doi: 10.1111/apt.12651.

Cercek, A., Lumish, M., Sinopoli, J. et al. (2022). PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med* 386 (25): 2363–2376. doi: 10.1056/NEJMoa2201445.

Chang, G.J., Rodriguez-Bigas, M.A., Skibber, J.M., and Moyer, V.A. (2007). Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 99: 433–441.

Chen, B., Scurrah, C.R., McKinley, E.T. et al. (2021). Differential pre-malignant programs and microenvironment chart distinct paths to malignancy in human colorectal polyps. *Cell* 184 (26): 6262–6280.e26. doi: 10.1016/j.cell.2021.11.031.

Chow, E., Lipton, L., Lynch, E. et al. (2006). Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. *Gastroenterology* 131 (1): 30–39. doi: 10.1053/j.gastro.2006.03.046.

Chung, D.C. and Rustgi, A.K. (2003). The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. *Ann Intern Med* 138 (7). doi: 10.7326/0003-4819-138-7-200304010-00012.

East, J.E., Atkin, W.S., Bateman, A.C. et al. (2017). British society of gastroenterology position statement on serrated polyps in the colon and rectum. *Gut* 2017 (66): 1181–1196.

Ekbom, A., Helmick, C., Zack, M., and Adami, H.O. (1990). Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 323 (18): 1228–1233. doi: 10.1056/NEJM199011013231802.

Fearon, E.R. and Vogelstein, B. (1990). A genetic model for colorectal tumorigenesis. *Cell* 61 (5): 759–767. doi: 10.1016/0092-8674(90)90186-i.

Fodde, R., Kuipers, J., Rosenberg, C. et al. (2001). Mutations in the APC tumor suppressor gene cause chromosomal instability. *Nat Cell Biol* 3 (4): 433–438. doi: 10.1038/35070129.

Friedl, W., Caspari, R., Sengteller, M. et al. (2001). Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. *Gut* 48 (4): 515–521. doi: 10.1136/gut.48.4.515.

Galandiuk, S., Rodriguezjusto, M., Jeffery, R. et al. (2012). Field cancerization in the intestinal epithelium of patients with Crohn's ileocolitis. *Gastroenterology* 142 (4): 855–864.e8. doi: 10.1053/j.gastro.2011.12.004.

Gandhi, J., Davidson, C., Hall, C. et al. (2017). Population-based study demonstrating an increase in colorectal cancer in young patients. *Br J Surg* 104 (8): 1063–1068. doi: 10.1002/bjs.10518.

Giardiello, F.M., Hamilton, S.R., Krush, A.J. et al. (1993). Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *New Engl J Med* 328 (18): 1313–1316. doi: 10.1056/NEJM199305063281805.

Gillen, C.D., Walmsley, R.S., Prior, P. et al. (1994). Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut* 35 (11): 1590–1592. doi: 10.1136/gut.35.11.1590.

Guinney, J., Dienstmann, R., Wang, X. et al. (2015). The consensus molecular subtypes of colorectal cancer. *Nature Med* 21 (11): 1350–1356. doi: 10.1038/nm.3967.

Guyot D'Asnières De Salins, A., Tachon, G., Cohen, R. et al. (2021). Discordance between immunochemistry of mismatch repair proteins and molecular testing of microsatellite instability in colorectal cancer. *ESMO open* 6 (3): 100120. doi: 10.1016/j.esmoop.2021.100120.

Haggitt, R.C., Glotzbach, R.E., Soffer, E.E., and Wruble, L.D. (1985). Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 89: 328–336.

He, T.C., Sparks, A.B., Rago, C. et al. (1998). Identification of c-MYC as a target of the APC pathway. *Science* 281 (5382): 1509–1512. doi: 10.1126/science.281.5382.1509.

Hermanek, P., Merkel, S., and Hohenberger, W. (2013). Prognosis of rectal carcinoma after multimodal treatment: ypTNM classification and tumor regression grading are essential. *Anticancer Res* 33: 559–566.

Hitchins, M., Williams, R., Cheong, K. et al. (2005). MLH1 germline epimutations as a factor in hereditary nonpolyposis colorectal cancer. *Gastroenterology* 129 (5): 1392–1399. doi: 10.1053/j.gastro.2005.09.003.

Hyman, N.H., Anderson, P., and Blasyk, H. (2004). Hyperplastic polyposis and the risk of colorectal cancer. *Diseases of the Colon and Rectum* 47 (12): 2101–2104. doi: 10.1007/s10350-004-0709-6.

Iino, H., Jass, J.R., Simms, L.A. et al. (1999). DNA microsatellite instability in hyperplastic polyps, serrated adenomas, and mixed polyps: a mild mutator pathway for colorectal cancer? *J Clin Pathol* 52 (1): 5–9. doi: 10.1136/jcp.52.1.5.

Isella, C., Brundu, F., Bellomo, S.E. et al. (2017). Selective analysis of cancer-cell intrinsic transcriptional traits defines novel clinically relevant subtypes of colorectal cancer. *Nat Comm* 8 (May): 1–16. doi: 10.1038/ncomms15107.

Jiri, J., Marketa, U., Arnoud, B. et al. (2022). Mutational analysis of driver genes defines the colorectal adenoma: in situ carcinoma transition. *Sci Rep* 12 (1): 1–10. doi: 10.1038/s41598-022-06498-9.

Jones, S., Chen, W.D., Parmigiani, G. et al. (2008). Comparative lesion sequencing provides insights into tumor evolution. *Proceedings of the National Academy of Sciences of the United States of America* 105 (11): 4283–4288. doi: 10.1073/pnas.0712345105.

Jover, R., Zapater, P., Castells, A. et al. (2009). The efficacy of adjuvant chemotherapy with 5-fluorouracil in colorectal cancer depends on the mismatch repair status. *Eur J Cancer* 45 (3): 365–373. doi: 10.1016/j.ejca.2008.07.016.

Kambara, T., Simms, L.A., Whitehall, V.L.J. et al. (2004). BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut* 53 (8): 1137–1144. doi: 10.1136/gut.2003.037671.

Kaplan, K.B., Burds, A.A., Swedlow, J.R. et al. (2001). A role for the Adenomatous Polyposis Coli protein in chromosome segregation. *Nat Cell Biol* 3 (4): 429–432. doi: 10.1038/35070123.

Kaz, A.M. and Brentnall, T.A. (2006). Genetic testing for colon cancer. *Nat Clin Pract Gastroenterol Hepatol* 3 (12): 670–679. doi: 10.1038/ncpgasthep0663.

Kikuchi, R., Takano, M., Takagi, K. et al. (1995). Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum* 38: 1286–1295.

Kim, J.C. and Bodmer, W.F. (2021). Genotypic and phenotypic characteristics of hereditary colorectal cancer. *Ann Coloproctol* 37 (6): 368–381. doi: 10.3393/ac.2021.00878.0125.

Koopman, M., Kortman, G.A.M., Mekenkamp, L. et al. (2009). Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer* 100 (2): 266–273. doi: 10.1038/sj.bjc.6604867.

Kopetz, S., Grothey, A., Yaeger, R. et al. (2019). Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *N Engl J Med* 381: 1632–1643. doi: 10.1056/NEJMoa1908075.

Lal, G. and Gallinger, S. (2000). Familial adenomatous polyposis. *Seminars in Surgical Oncology* 18 (4): 314–323. 10.1002/(SICI)1098-2388(200006)18:4<314::AID-SSU6>3.0.CO;2-9.

Lal, N., Chan, D.K.H., Ng, M.E. et al. (2022). Primary tumour immune response and lymph node yields in colon cancer. *Br J Cancer* doi: 10.1038/s41416-022-01700-1.

Lamb, C.A., Kennedy, N.A., Raine, T. et al. (2019). British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 68 (Suppl 3): s1–s106. doi: 10.1136/gutjnl-2019-318484.

Lamberti, C., Mangold, E., Pagenstecher, C. et al. (2006). Frequency of hereditary non-polyposis colorectal cancer among unselected patients with colorectal cancer in Germany. *Digestion* 74 (1): 58–67. doi: 10.1159/000096868.

Langer, R. and Becker, K. (2018). Tumor regression grading of gastrointestinal cancers after neoadjuvant therapy. *Virchows Arch* 472: 175–178.

Lash, R.H., Genta, R.M., and Schuler, C.M. (2010). Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. *J Clin Pathol* 63: 681–686.

Latham, A., Srinivasan, P., Kemel, Y. et al. (2019). Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer. *J Clin Oncol* 37 (4): 286–295. doi: 10.1200/JCO.18.00283.

Le, D.T., Durham, J.N., Smith, K.N. et al. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 357: 409–413.

Le, D.T., Uram, J.N., Wang, H. et al. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *New Engl J Med* 372 (26): 2509–2520. doi: 10.1056/nejmoa1500596.

Leggett, B. and Whitehall, V. (2010). Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 138 (6): 2088–2100. doi: 10.1053/j.gastro.2009.12.066.

Leppert, M., Burt, R., Hughes, J.P. et al. (1990). Genetic analysis of an inherited predisposition to colon cancer in a family with a variable number of adenomatous polyps. *New Engl J Med* 322 (13): 904–908. doi: 10.1056/NEJM199003293221306.

Lin, J.S., Perdue, L.A., Henrikson, N.B. et al. (2021). Screening for colorectal cancer: updated evidence report and systematic review for US preventive services task force. *JAMA* 20 326 (3): 279.

Lindor, N.M., Rabe, K., Petersen, G.M. et al. (2005). Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *J Am Med Ass* 293 (16): 1979–1985. doi: 10.1001/jama.293.16.1979.

Linnebacher, M., Gebert, J., Rudy, W. et al. (2001). Frameshift peptide-derived T-cell epitopes: a source of novel tumor-specific antigens. *Int J Cancer* 93 (1): 6–11. doi: 10.1002/ijc.1298.

Loughrey, M.B., Quirke, P., and Shepherd, N.A. (2018). The Royal college of pathologists dataset for histopathological reporting of colorectal cancer.

Loughrey, M.B., Webster, F., Arends, M.J. et al. (2022 March 1). Dataset for pathology reporting of colorectal cancer: recommendations from the international collaboration on cancer reporting (ICCR). *Ann Surg* 275 (3): e549–e561.

Lugli, A., Zlobec, I., Berger, M.D. et al. (2021). Tumor budding in solid cancers. *Nat Rev Clin Oncol* 18 (2): 101–115.

Lynch, H.T. and Lynch, J.F. (1985). Hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II): a common genotype linked to oncogenes? *Med Hypotheses* 18 (1): 19–28. doi: 10.1016/0306-9877(85)90115-X.

Maas, M., Nelemans, P.J., Valentini, V. et al. (2010). Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 11: 835–844.

McLellan, E.A., Owen, R.A., Stepniewska, K.A. et al. (1993). High frequency of K-ras mutations in sporadic colorectal adenomas. *Gut* 34 (3): 392–396. doi: 10.1136/gut.34.3.392.

Meric-Bernstam, F., Hurwitz, H., Raghav, K.P.S. et al. (2019). Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 20: 518–530. doi: 10.1016/S1470-2045(18)30904-5.

Monahan, K.J., Bradshaw, N., Dolwani, S. et al. (2020). Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut* 69 (3): 411–444. doi: 10.1136/gutjnl-2019-319915.

Mori, Y., Nagse, H., Ando, H. et al. (1992). Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Human Mol Genet* 1 (4): 229–233. doi: 10.1093/hmg/1.4.229.

Morton, D.G., Gibson, J., Macdonald, F. et al. (2005). Role of congenital hypertrophy of the retinal pigment epithelium in the predictive diagnosis of familial adenomatous polyposis. *Br J Surg* 79 (7): 689–693. doi: 10.1002/bjs.1800790733.

Munro, A.J., Lain, S., and Lane, D.P. (2005). P53 abnormalities and outcomes in colorectal cancer: a systematic review. *Br J Cancer* 92 (3): 434–444. doi: 10.1038/sj.bjc.6602358.

Murphy, K.M., Zhang, S., Geiger, T. et al. (2006). Comparison of the microsatellite instability analysis system and the Bethesda panel for the determination of microsatellite instability in colorectal cancers. *J Mol Diagn* 8 (3): 305–311. doi: 10.2353/jmoldx.2006.050092.

Nagtegaal, I.D., Knijn, N., Hugen, N. et al. (2016). Tumor deposits in colorectal cancer: improving the value of modern staging-A systematic review and meta-analysis. *J Clin Oncol* 35: 1119–1127.

Nagtegaal, I.D., van de Velde, C.J., van der Worp, E. et al. (2002). Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 20: 1729–1734.

Nalapareddy, K., Nattamai, K.J., Kumar, R.S. et al. (2017). Canonical Wnt signaling ameliorates aging of intestinal stem cells. *Cell Reports* 18 (11): 2608–2621. doi: 10.1016/j.celrep.2017.02.056.

Narayan, S. and Roy, D. (2003). Role of APC and DNA mismatch repair genes in the development of colorectal cancers. *Mol Cancer* 2: 1–15. doi: 10.1186/1476-4598-2-41.

National Institute for Health and Care Excellence (NICE) (2017). Molecular testing strategies for Lynch syndrome in people with colorectal cancer. Nice (February 2017): 1–37. Retrieved from https://www.nice.org.uk/guidance/dg27 (accessed 28 July 2022).

Nieminen, T.T., O'Donohue, M.F., Wu, Y. et al. (2014). Germline mutation of RPS20, encoding a ribosomal protein, causes predisposition to hereditary nonpolyposis colorectal carcinoma without DNA mismatch repair deficiency. *Gastroenterology* 147 (3): 595–598.e5. doi: 10.1053/j.gastro.2014.06.009.

O'Brien, M.J., Yang, S., Mack, C. et al. (2006). Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol* 30 (12): 1491–1501. doi: 10.1097/01.pas.0000213313.36306.85.

O'Connor, P.M., Lapointe, T.K., Beck, P.L., and Buret, A.G. (2010). Mechanisms by which inflammation may increase intestinal cancer risk in inflammatory bowel disease. *Inflamm Bowel Dis* 16 (8): 1411–1420. doi: 10.1002/ibd.21217.

Orford, K., Crockett, C., Jensen, J.P. et al. (1997). Serine phosphorylation-regulated ubiquitination and degradation of β- catenin. *J Biol Chem* 272 (40): 24735–24738. doi: 10.1074/jbc.272.40.24735.

Overman, M.J., McDermott, R., Leach, J.L. et al. (2017). Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 18 (9): 1182–1191. doi: 10.1016/S1470-2045(17)30422-9.

Peltomäki, P., Lothe, R.A., Aaltonen, L.A. et al. (1993). Microsatellite instability is associated with tumors that characterize the hereditary non-polyposis colorectal carcinoma syndrome. *Cancer Res* 53 (24): 5853–5855. http://www.ncbi.nlm.nih.gov/pubmed/8261393.

Pietrantonio, F., Petrelli, F., Coinu, A. et al. (2015). Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 51: 587–594.

Popat, S., Hubner, R., and Houlston, R.S. (2005). Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol: Off J Am Soc Clin Oncol* 23 (3): 609–618. doi: 10.1200/JCO.2005.01.086.

Popat, S. and Houlston, R.S. (2005). A systematic review and meta-analysis of the relationship between chromosome 18q genotype, DCC status and colorectal cancer prognosis. *Eur J Cancer* 41 (14): 2060–2070. doi: 10.1016/j.ejca.2005.04.039.

Qazi, T.M., O'Brien, M.J., Farraye, F.A. et al. (2014 December). Epidemiology of goblet cell and microvesicular hyperplastic polyps. *Am J Gastroenterol* 109 (12): 1922–1932.

Quirke, P., Steele, R., Monson, J. et al. (2009). Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 373: 821–828.

Radtke, F. and Clevers, H. (2005). Self-renewal and cancer of the gut: two sides of a coin. *Science* 307 (5717): 1904–1909. doi: 10.1126/science.1104815.

Rosenberg, D.W., Yang, S., Pleau, D.C. et al. (2007). Mutations in BRAF and KRAS differentially distinguish serrated versus non-serrated hyperplastic aberrant crypt foci in humans. *Cancer Res* 67 (8): 3551–3554. doi: 10.1158/0008-5472.CAN-07-0343.

Rozek, L.S., Schimit, S.L., Greenson, J.K. et al. (2016 May 12). Tumor infiltrating lymphocytes, Crohn's-like lymphoid reaction and survival from colorectal cancer. *J Nat Cancer Inst* 108 (8).

Sangiorgi, E. and Capecchi, M.R. (2008). Bmi1 is expressed in vivo in intestinal stem cells. *Nat Genet* 40 (7): 915–920. doi: 10.1038/ng.165.

Sartore-Bianchi, A., Trusolino, L., Martino, C. et al. (2016). Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 17: 738–746. doi: 10.1016/S1470-2045(16)00150-9.

Schumacher, T.N. and Schreiber, R.D. (2015). Neoantigens in cancer immunotherapy. *Science* 348 (6230): 69–74. doi: 10.1126/science.aaa4971.

Setti-Carraro, P. and Nicholls, R.J. (1996). Choice of prophylactic surgery for the large bowel component of familial adenomatous polyposis. *Br J Surg* 83 (7): 885–892. doi: 10.1002/bjs.1800830704.

Shih, I.M., Wang, T.L., Traverso, G. et al. (2001). Top-down morphogenesis of colorectal tumors. *Proceedings of the National Academy of Sciences of the United States of America* 98 (5): 2640–2645. doi: 10.1073/pnas.051629398.

Snippert, H.J., Schepers, A.G., Van Es, J.H. et al. (2014). Biased competition between Lgr5 intestinal stem cells driven by oncogenic mutation induces clonal expansion. *EMBO Rep* 15 (1): 62–69. doi: 10.1002/embr.201337799.

Snover, D.C., Jass, J.R., Fenoglio-Preiser, C., and Batts, K.P. (2005). Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. *Am J Clin Pathol* 124 (3): 380–391. doi: 10.1309/V2EPTPLJRB3FGHJL.

Spigelman, A.D., Talbot, I.C., Williams, C.B. et al. (1989). Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 334 (8666): 783–785. doi: 10.1016/S0140-6736(89)90840-4.

Spirio, L., Otterud, B., Stauffer, D. et al. (1992). Linkage of a variant or attenuated form of adenomatous polyposis coli to the adenomatous polyposis coli (APC) locus. *Am J Hum Genet* 51 (1): 92–100.

Stoffel, E.M. and Boland, C.R. (2015). Genetics and genetic testing in hereditary colorectal cancer. *Gastroenterology* 149 (5): 1191–1203.e2. doi: 10.1053/j.gastro.2015.07.021.

Syngal, S., Brand, R.E., Church, J.M. et al. (2015). ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 110 (2): 223–262. doi: 10.1038/ajg.2014.435.

Tanaka, T., Watanabe, T., Kazama, Y. et al. (2006). Chromosome 18q deletion and Smad4 protein inactivation correlate with liver metastasis: a study matched for T- and N- classification. *Br J Cancer* 95 (11): 1562–1567. doi: 10.1038/sj.bjc.6603460.

Tannin, L., Yin, J., Kozam, M. et al. (1995). Adenomatous polyposis coli gene mutations in ulcerative colitis-associated dysplasias and cancers versus sporadic colon neoplasms. *Cancer Res* 55 (10): 2035–2038.

ten Hoorn, S., de Back, T.R., Sommeijer, D.W., and Vermeulen, L. (2021). Clinical value of consensus molecular subtypes in colorectal cancer: a systematic review and meta-analysis. *JNCI: J Natl Cancer Inst* 00 (December 2020): 1–14. doi: 10.1093/jnci/djab106.

Tetsu, O. and McCormick, F. (1999). Beta-Catenin regulates expression of cyclinD1 in colon carcinomacells Osamu. *Nature* 398 (April): 422.

Thibodeau, S.N., Bren, G., and Schaid, D. (1993). Microsatellite instability in cancer of the proximal colon. *Science* 260 (5109): 816–819. doi: 10.1126/science.8484122.

Toyota, M., Ahuja, N., Ohe-Toyota, M. et al. (1999). CpG island methylator phenotype in colorectal cancer. *Proceedings of the National Academy of Sciences of the United States of America* 96 (15): 8681–8686. 10.1073/pnas.96.15.8681.

Ueno, H., Mochizuki, H., Hashiguchi, Y. et al. (2004). Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 127: 385–394.

Umar, A., Boland, C.R., Terdiman, J.P. et al. (2004). Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 96 (4): 261–268. doi: 10.1093/jnci/djh034.

Valle, L., Vilar, E., Tavtigian, S.V., and Stoffel, E.M. (2019). Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *J Pathol* 247 (5): 574–588. doi: 10.1002/path.5229.

Van Cutsem, E., Lenz, H.J., Köhne, C.H. et al. (2015 March 1). Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol* 33 (7): 692–700.

Vasen, H.F.A., Watson, P., Mecklin, J.P., and Lynch, H.T. (1999). New clinical criteria for hereditary nonpolyposis colorectal definition of HNPCC. *Gastroenterology* 116: 1453–1456.

Vermeulen, L., Morrissey, E., Van Der Heijden, M. et al. (2013). Defining stem cell dynamics in models of intestinal tumor initiation. *Science* 342 (6161): 995–998. doi: 10.1126/science.1243148.

Wasserman, I., Lee, L.H., Ogino, S. et al. (2019). Smad4 loss in colorectal cancer patients correlates with recurrence, loss of immune infiltrate, and chemoresistance. *Clin Cancer Res* 25 (6): 1948–1956. doi: 10.1158/1078-0432.CCR-18-1726.

WHO classification of tumors (2019). *Digestive System Tumors*, 5e.

Williams, J.G., Pullan, R.D., Hill, J. et al. (2013). Management of the malignant colorectal polyp: ACPGBI position statement. *Colorectal Dis* 15 (Suppl 2): 1–38. doi: 10.1111/codi.12262.

Winawer, S.J., Fletcher, R.H., Miller, L. et al. (1997). Colorectal cancer screening: clinical guidelines and rationale the Adenoma-Carcinoma sequence. *Gastroenterology* 112: 594–642.

Winther, K.V., Jess, T., Langholz, E. et al. (2004). Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2 (12): 1088–1095. doi: 10.1016/s1542-3565(04)00543-9.

Worthley, D.L., Whitehall, V.L.J., Buttenshaw, R.L. et al. (2010). DNA methylation within the normal colorectal mucosa is associated with pathway-specific predisposition to cancer. *Oncogene* 29 (11): 1653–1662. doi: 10.1038/onc.2009.449.

Yan, H.H.N., Lai, J.C.W., Ho, S.L. et al. (2017). RNF43 germline and somatic mutation in serrated neoplasia pathway and its association with BRAF mutation. *Gut* 66 (9): 1645–1656. doi: 10.1136/gutjnl-2016-311849.

Yang, J.F., Tang, S.J., Lash, R.H. et al. (2015 March). Anatomic distribution if sessile serrated adenoma/polyp with and without cytologic dysplasia. *Arch Pathol Lab Med* 139 (3): 388–393.

Yang, S., Farraye, F.A., Mack, C. et al. (2004). BRAF and KRAS mutations in hyperplastic polyps and serrated adenomas of the colorectum: relationship to histology and CpG island methylation status. *Am J Surg Pathol* 28 (11): 1452–1459. doi: 10.1097/01.pas.0000141404.56839.6a.

Yin, J., Harpaz, N., Tong, Y. et al. (1993). p53 Point mutations in dysplastic and cancerous ulcerative colitis lesions. *Gastroenterology* 104 (6): 1633–1639. doi: 10.1016/0016-5085(93)90639-T.

Zhou, S., Buckhaults, P., Zawel, L. et al. (1998). Targeted deletion of Smad4 shows it is required for transforming growth factor β and activin signaling in colorectal cancer cells. *Proceedings of the National Academy of Sciences of the United States of America* 95 (5): 2412–2416. doi: 10.1073/pnas.95.5.2412.

Zhu, L., Gibson, P., Currle, D.S. et al. (2009). Prominin 1 marks intestinal stem cells that are susceptible to neoplastic transformation. *Nature* 457 (7229): 603–607. doi: 10.1038/nature07589.

11 Screening, Surveillance, and Prevention for Colorectal Cancer

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[Aspects of the epidemiology of colorectal cancer are also covered in Chapter 1 and Chapter 9. Aspects of gastrointestinal screening and surveillance are also covered in Chapter 3].

Screening for Colorectal Cancer

Epidemiology of Colorectal Cancer

On a global scale, colorectal cancer is the third most common cancer in terms of incidence, and second in terms of mortality, being responsible for approximately 900,000 annual deaths (Bray et al. 2018; Dekker et al. 2019). Based on 2017–2019 data from the Surveillance, Epidemiology, and End Results program (SEER, USA), approximately 4.1 percent of men and women will be diagnosed with colorectal cancer at some point during their lifetime (National Cancer Institute 2022). In its Annual Report to the Nation, the SEER indicates that the age-standardized, delay-adjusted incidence rate of colorectal cancer is 44.6 (44.5 to 44.8) per 100,000 inhabitants, with an age-standardized death rate of 16.3 (16.2 to 16.4) per 100,000 (Islami et al. 2021).

The Principles of Screening for Colorectal Cancer

Currently, three pathways leading from normal bowel mucosa to colorectal cancer have been identified: the adenoma–carcinoma pathway, the serrated pathway and the inflammatory pathway, which is defined by progressing dysplasia due to chronic inflammation ultimately leading to colorectal cancer, as encountered in patients with inflammatory bowel disease (Keum and Giovannucci 2019).

Based on 2012–2018 SEER data, at initial presentation, 37% of colorectal cancers are localized (stages I and II), 36% have regional spread (stage III) and 22% have distant spread (stage IV). The 5-year overall survival for colorectal cancer is 65.1%. Of interest, the 5-year overall survival is 90.9% for localized colorectal cancer (stages I and II), 72.8% for stage III and 15.1% for stage IV (National cancer institute 2022). The TNM stage is the main predictor of survival for colorectal cancer.

Patients with colorectal cancer may develop symptoms, such as rectal bleeding (odds ratio (OR) for colorectal cancer: 20), change in bowel habit (OR: 14), abdominal pain (OR: 3.9), diarrhea (OR: 2.4), constipation (OR: 2.1) or weight loss (OR: 1.2–2.5) (Hamilton et al. 2009). However, colorectal cancer rarely causes symptoms in its early stage, and available evidence suggests that using the symptomatic route to identify patients with colorectal cancer is not particularly fruitful (Ahmed et al. 2005). Therefore, an alternative method of consistently detecting early disease is achieved by screening at-risk populations.

According to the criteria of Wilson and Jungner (Wilson et al. 1968), there is little doubt that colorectal cancer is a suitable candidate for screening. The treatment for colorectal cancer is evidence-based, and the natural history is reasonably well understood; the evidence for the adenoma–carcinoma sequence is strong and it is generally accepted that the majority of invasive cancers arise from pre-existing adenomatous polyps. Therefore, if screening detects significant adenomas, there is an opportunity to reduce the incidence of colorectal cancer. It is also well documented that the prognosis for colorectal cancer is highly dependent on stage at diagnosis. However, the most important evidence supporting screening for colorectal cancer comes from population-based randomized trials.

Therefore, screening for colorectal cancer is based on these two principles:

1 Identifying precursor lesions, such as adenomas, serrated lesions, and hamartomatous polyps such as juvenile and Peutz-Jeghers polyps ((WHO) WHO 2019), in order to remove them and avoid future progression to colorectal cancer (prevention, in order to decrease the incidence of colorectal cancer).

2 Detecting colorectal cancer at an earlier stage, in order to improve the outcomes of treatment (screening, in order to identify cancer cases at a localized stage).

Over the last 40 years in Europe, countries that had the largest reduction in colorectal cancer mortality were those with

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better access to screening services and specialized care (Ait Ouakrim et al. 2015).

Methods for Screening for Colorectal Cancer

Currently, tests for screening for colorectal cancer are classified into fecal tests, endoscopy techniques, and imaging techniques.

Fecal Tests

The most widely used fecal tests for screening of colorectal cancer look for microscopic blood in the feces. The most common are the guaiac fecal occult blood test (gFOBT), the fecal immunochemical test (iFOBT or FIT) and the multitargeted fecal DNA test (FIT-DNA or sDNA).

gFOBT consists in placing a fecal sample on a paper containing a chemical extracted from the resin of Guaiacum tree, and adding hydrogen peroxide. If the fecal sample contains heme, either in its free form or bound to proteins such as globin, myoglobin and some cytochromes, the test turns blue (positive). The most commonly used gFOBT is the Haemoccult II test. gFOBT has limited sensitivity for identifying patients with colorectal cancer in a screened population, with some studies reporting a sensitivity of only 7.2% using colonoscopy as a gold standard (Wong et al. 2012). Moreover, the test has several limitations. First, gFOBT is not capable of detecting the degradation products of heme. As the heme circulates through the gastrointestinal tract, it is modified by microflora and loses its peroxidase activity. Therefore, gFOBT is more sensitive for distal lesions than for proximal lesions (Wong et al. 2012), and its sensitivity can be altered if the cancer is not bleeding or bleeding intermittently. Reyhdration of the guaiac test increases its sensitivity by lysing red cells and exposing more heme. However, although this approach will detect more colorectal cancers it will also detect blood from relatively trivial lesions and this has an adverse effect on specificity. Second, gFOBT can yield false positive results in the context of recent intake of dietary meat or vegetables containing hemoglobin, myoglobin, or peroxidase (such as red meat, broccoli, cauliflower, radish, and others). It has been suggested that specificity can be improved by appropriate dietary restriction, but a meta-analysis suggested this approach to be ineffective (Pignone et al. 2001). In terms of efficiency, gFOBT allows decreasing colorectal cancer mortality in screened groups. For instance, biennial screening and annual screening using Haemoccult II, associated with colonoscopy in patients with positive test, led to a drop in mortality of 21% in the biennial group and of 33% in the annual group after a follow-up period of 18 years (Mandel et al. 1993). Moreover, the incidence of colorectal cancer in the groups offered screening dropped significantly below that in the control group, probably due to colonoscopic polypectomy (Mandel et al. 2000). This reduction of mortality induced by screening using Haemoccult II was also shown by other teams. For instance, biennial screening allowed a 15% reduction in death rate from colorectal cancer after a median of 7.8 years of follow-up (Hardcastle et al. 1996). At a median of 11 years of follow-up this reduction in mortality was still seen, albeit reduced to 13% (Scholefield et al. 2002). Moreover, screening allowed reducing the incidence of emergency admissions for colorectal cancer, which may have important economic significance for healthcare systems (Scholefield et al. 1998). However, Haemoccult sensitivity was only 50%, and therefore a significant number of colorectal cancers were missed (Hardcastle et al. 1996). Other studies confirmed the reduction in mortality conferred by screening using gFOBT (Faivre et al. 2004; Jorgensen et al. 2002) and the moderate sensitivity of the test for detection of colorectal cancer (Malila et al. 2008) and advanced adenomas (Lin et al. 2021). Another study with a large sample size confirmed that the number of positive tests in a screened population ranged from 1.2 to 2.1%, that the positive predictive value of the test for detecting colorectal cancer ranged between 13.9 to 18.7%, and that screening using gFOBT allowed a reduction of 33% in colorectal cancer mortality. Moreover, among responders, the sensitivity of the test was 68.8% (Faivre et al. 2004). Acceptance of the test usually ranges between 50 to more than 90% (Faivre et al. 2004; Jorgensen et al. 2002; Kewenter et al. 1994; Malila et al. 2008). In meta-analysis, annual or biennial gFOBT screening allowed reduction of colorectal cancer-specific mortality (relative risk at 19.5 years: 0.91, relative risk at 30 years: 0.78) after 2 to 9 rounds of screening (Lin et al. 2021). Therefore, although the gFOBT is fairly insensitive and patient’s compliance is relatively poor, early detection of colorectal cancer by screening using gFOBT is beneficial.

Most of the research on fecal occult blood test screening for colorectal cancer has employed the gFOBT. Since then, a newer test has emerged, identifying globin using antibodies: the FIT. The FIT has several advantages over gFOBT, including notably a better sensitivity (Lin et al. 2021; Shapiro et al. 2017; van Rossum et al. 2008) and the absence of dietary requirements. Nationwide screening revealed that FIT allowed reaching a 34% reduction in the incidence of advanced colorectal cancer, and a 40% reduction in colorectal cancer-related mortality. As for gFOBT, the test was more efficient for distal lesions than for proximal ones (Chiu et al. 2021). Moreover, FIT allows adjustment of the positivity cut-off value and, therefore, of the balance between sensitivity and specificity (D’Souza et al. 2021; Guittet et al. 2007), which may be of interest depending on the risk of the screened population. For instance, in patients with symptoms of colorectal cancer and referred to the United Kingdom two weeks’ wait pathway, the sensitivity of the test is maximized to 97% using a cut-off value of 2 µg/g which allows ruling out colorectal cancer in this high-risk population and avoiding unnecessary investigations (D’Souza et al. 2021). In patients with a personal or familial history of colorectal cancer, FIT was shown by meta-analysis to have a sensitivity for detecting colorectal cancer of 93% and a specificity of 91%. The best combination between sensitivity and specificity was demonstrated for a test cut-off between 15 and 25µg/g in faeces (Katsoula et al. 2017). The better accuracy of FIT when compared to gFOBT has led the American College of Gastroenterology to recommend favoring FIT over gFOBT (Rex et al. 2009), and FIT testing is now incorporated within the United Kingdom national bowel cancer screening program.

More recently, FIT-DNA has emerged as a new alternative for performing fecal occult blood testing. FIT-DNA detects both blood in the stool (FIT component) and DNA mutations in genes associated with colorectal cancer. The DNA comes from cells in the lining of the colon and rectum that are shed and collected in feces as it passes through the large intestine and rectum. DNA is extracted from stool samples and amplified using polymerase chain reaction. However, because of the heterogeneity of genetic mutations in both cancers and adenomas, developing a test that will be reasonably sensitive it is essential to look at a panel of different mutations in the different genes. The genes most commonly studied are *Kras, APC* and *p53*, and the mononucleotide BAT26 has been used as a marker of microsatellite instability. It is also possible to use DNA non-specifically, in the sense that "long DNA" is likely to be shed from tumors, whereas cells shed from the colonic epithelium undergoing apoptosis give rise to short segments of DNA.

Meta-analysis showed that FIT-DNA has a pooled sensitivity of 93% and pooled specificity of 85% for detecting colorectal cancer, and a pooled sensitivity of 43% and a pooled specificity of 89% for detecting advanced adenomas (Lin et al. 2021). FIT-DNA was reported to have better sensitivity for detecting colorectal cancer (92.3% versus 73.8%) and advanced precancerous lesions (42.4% versus 23.8%) than FIT. However, FIT-DNA has several limitations, among which is a complicated sample collection, the necessity of performing the analyses externally, a decreased specificity when compared to FIT (Imperiale et al. 2014) and a higher cost (Hoffman et al. 2021). Simulation modelling found FIT-DNA to be less effective and more expensive than FIT and colonoscopy for screening purpose (Ladabaum and Comparative Effectiveness 2016).

Serum Tests

Serum tests detect circulating DNA in the blood. One study, which evaluated the Epi proColon test identifying methylated *SEPT9* DN, reported a sensitivity and a specificity of, respectively, 68% and 79% for detecting colorectal cancer (Potter et al. 2014). This test suffers from lower sensitivity than FOBT tests, and may constitute an alternative in patients non-compliant with standard screening methods.

Flexible Sigmoidoscopy

Considering that approximately three-quarters of colorectal cancers are located in the sigmoid colon and rectum, it seems reasonable to use flexible sigmoidoscopy as a screening tool, particularly as the finding of a significant distal adenoma (see Figure 1) may act as an indicator of more proximal disease. Based on these premises, it has been initially proposed that a single flexible sigmoidoscopy at about the age of 60 years with removal of all adenomas at the time of examination and performing colonoscopy for this at high risk for adenoma or cancer would be an effective screening modality for colorectal cancer (Atkin et al. 2001). In addition, this strategy might be expected to reduce the incidence of colorectal cancer by removal of adenomas. Compliance with screening using sigmoidoscopy was reported to range between 46.6% and 71% (Atkin et al. 2017; Segnan et al. 2011; Verne et al. 1998). This compliance could be increased from 46.6% to 61.8% when associated with telephone reminders (Verne et al. 1998). In terms of findings, polyps are found in 19.3%, adenomas in 6.8% and colorectal cancer in 0.4% of sigmoidoscopies performing in patients aged 50–75 years (Verne et al. 1998). Screening using flexible sigmoidoscopy with a repetition at year three or five was demonstrated to decrease the incidence of colorectal cancer (relative risk: 0.82) and mortality (relative risk: 0,75) after approximately 16 years when compared to usual care. This reduction of mortality was limited to the distal colon, where sigmoidoscopy allowed early detection of precursor lesions and cancer (Miller et al. 2019). In per protocol analysis, reduction of the incidence (by 31–35%) and the mortality (by 38–43%) in patients screened by flexible sigmoidoscopy when compared to non-screened patients was confirmed by other randomized controlled trials,

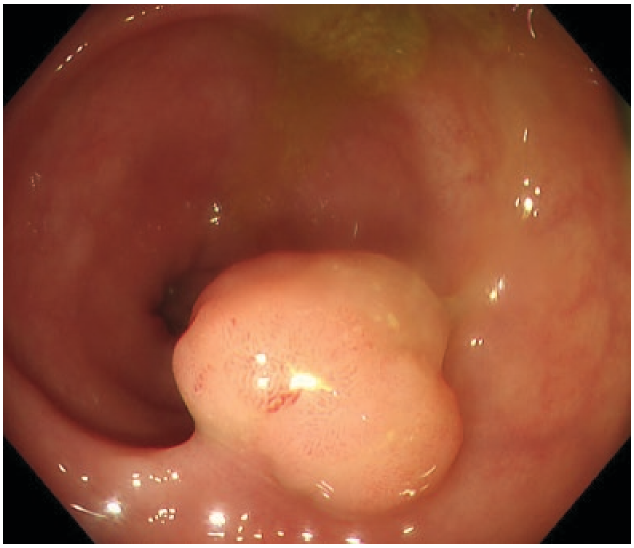

Figure 1 Adenoma detected during colorectal cancer screening using flexible sigmoidoscopy.

even if the examination was performed only once (Atkin et al. 2010; Atkin et al. 2017; Holme et al. 2014; Segnan et al. 2011). In England, national flexible sigmoidoscopy screening has recently been stopped in favor of initial FIT testing and recommendation for a colonoscopy for patients who are FIT-positive.

Colonoscopy

Colonoscopy itself would, on the surface, appear to be the ideal screening tool as it ought to have a specificity approaching 100% and a very high sensitivity. That sensitivity is not 100% is evidenced by a study in which back-to-back colonoscopies clearly demonstrated that adenomas and occasionally carcinomas can be missed even by the most experienced colonoscopists (Rex et al. 1997). Sensitivity of “blinded” colonoscopy (without knowledge of preliminary results of CT colonography) was estimated to be of 87.5%, 91.5% and 92.3% for polyps of diameters of 10mm, 8mm, and 6mm, respectively (Pickhardt et al. 2003). Compliance with the screening program was evaluated to range between 22.9% to 60.7%, 77.3% of patients did not need any sedation, and colonoscopy was complete (cecal intubation) in 97.2% of patients (Bretthauer et al. 2016). Screening colonoscopy allows detection of colorectal cancer in 0.5% of patients, adenomas in 30.7% and high-risk adenomas in 10.4% (Bretthauer et al. 2016). A non-randomized prospective study from the USA reported a reduction in the incidence of colorectal cancer (risk difference ranging between -0.42% to -0.14%) and in the mortality in patients subjected to colonoscopy screening versus patients not subjected to screening (Garcia-Albeniz et al. 2017).

When compared to other screening modalities, colonoscopy performs well but suffers from low uptake. For instance, a randomized controlled trial, including approximately 30,000 subjects, compared screening using 4 rounds of FIT (and colonoscopy if positive), once-only flexible sigmoidoscopy (and completion colonoscopy if worrisome findings) and once-only colonoscopy. Of note, compliance with the screening program was higher for FIT (73%) and lower for flexible sigmoidoscopy (31%) and colonoscopy (24%). As a corollary, in intention-to-treat screen analysis, FIT allowed identifying more cases of advanced colorectal neoplasia (4.5%) than both flexible sigmoidoscopy (2.3%) and colonoscopy (2.2%). When looking at patients who received screening (per protocol analysis), colonoscopy was the most efficient screening modality (9.1% of advanced colorectal neoplasia), followed by flexible sigmoidoscopy (7.4%) and FIT (6.1%). Finally, both endoscopic techniques led to less false negative results. For instance, interval colorectal cancer was found in 0.13% of patients with negative FIT, when compared to 0.09% after negative flexible sigmoidoscopy and 0.01% after negative colonoscopy (Grobbee et al. 2020).

Nowadays, colonoscopy is not used as a first-line screening tool in many countries, mostly due to its costs, the increased risks when compared to less invasive methods and its availability. Screening colonoscopy only represents approximately 10% of colonoscopies performed in the United Kingdom (Gavin et al. 2013).

Radiology

CT colonography consists of a low-dose CT combined with CO^2 insufflation of the colon. The sensitivity of CT colonography depends on the size of the lesion to be identified. For instance, its sensitivity is 93.8% for polyps >10mm but only of 88.7% for polyps >6mm (Pickhardt et al. 2003). A randomized controlled trial compared screening using CT colonography (completed by colonoscopy if needed) with screening using colonoscopy. Participation was 22% for colonoscopy and 34% for CT colonography. CT colonography identified advanced colorectal neoplasia in 6.1% of participants versus 8.7% of participants who received colonoscopy. In intention to screen analysis (looking at patients invited for screening and not at patients who received screening), CT colonography diagnosed more advanced colorectal neoplasia (2.1%) than colonoscopy (1.9%) (Stoop et al. 2012). CT colonography is usually indicated for colorectal cancer screening in patients refusing a more invasive procedure, and does involve radiation exposure.

Indications for Screening for Colorectal Cancer

Accepted criteria for an effective screening program are attributed to Wilson and Jungner (Wilson et al. 1968), and were then refined to include consideration of the at risk population to be screened (Dobrow et al. 2018). The current recommendation is to perform screening for colorectal cancer in patients with an estimated risk of colorectal cancer of at least 3% in 15 years (Helsingen et al. 2019).

This risk can be evaluated by following guidelines, such as the NICE NG12 guideline, or by using risk prediction models, such as the Qcancer calculator, the Bristol–Birmingham equation, the COLONPREDICT model, the FAST model, the CAPER score, and others (Helsingen et al. 2019; Herrero et al. 2018; Jeon et al. 2018; Marshall et al. 2011). Estimation of the risk does not only allow identifying subjects to screen, but also to choose the most appropriate methods for screening, in terms of diagnostic accuracy, risks of harm and cost (Hull et al. 2020).

In an average risk population (patients without inflammatory bowel disease and/or familial history of colorectal cancer), age constitutes the main risk factor for colorectal cancer, and therefore most screening programs are based on an age criterion. For example, the US Preventive Services Task Force (USPSTF) recommends performing screening for colorectal cancer in patients aged 50–75 years (grade A recommendation), in those aged 45–49 years (grade B recommendation) and in selected patients aged 76–85 years (grade C recommendation) (Uspst et al. 2021). Most

American professional societies recommend to start screening for colorectal cancer at the age of 45–50 until 75 (Kanth and Inadomi 2021). The United Kingdom Bowel Cancer Screening Program (BCSP) provides screening for colorectal cancer every two years to patients aged 60 to 74 years (although the lower age range is planned to reduce incrementally) using FIT and, in patients with positive test, a subsequent colonoscopy (Committee UNS).

There is great diversity in terms of modalities used in national screening programs (Shaukat and Levin 2022) or recommended by professional societies (Kanth and Inadomi 2021), but nowadays usual testing involves performing FIT annually of biennially, or performing a single sigmoidoscopy or colonoscopy. If one of these examinations yields positive results, complete assessment of the lower gastrointestinal tract is performed using colonoscopy (Helsingen et al. 2019). Simulation model comparing these four screening strategies in a population with a 15-year colorectal cancer risk ranging between 1 to 7% reported a similar reduction in mortality for annual FIT, biennial FIT, single sigmoidoscopy and single colonoscopy (Buskermolen et al. 2019).

Disadvantages of Screening

Although performing a FIT test is without hazard and flexible sigmoidoscopy is a safe investigation, subsequent colonoscopy has the potential to cause morbidity and even mortality. Of note, the perforation rate due to colonoscopy ranges between 0.005 and 0.085% (Kim et al. 2019). In addition to this, false-negative FOBT results are inevitable owing to the relatively low sensitivity of this investigation and there is concern that a negative result may falsely reassure an individual to such an extent that they may ignore symptoms and delay the diagnosis of colorectal cancer (“the certificate of health effect”). FIT testing does benefit from a higher sensitivity than FOBT. Finally, CT colonography exposes patients to radiation and may lead to the development of cancer, and is limited by its cost and the expertise of the radiologist (Plumb et al. 2014). Whilst very rare, perforation has also been reported after CT colonography.

Bias of Screening

The benefits of screening are seemingly obvious, but screening is associated with inbuilt biases that result in screen-detected disease being associated with a better prognosis than symptomatic disease regardless of whether or not the screening process has actually affected the outcome.

These biases are volunteer bias, length bias, and lead-time bias. Volunteer bias results from the fact that invitations to be screened are more likely to be accepted by those who are health conscious than those who are not. Therefore, people who accept invitations to be screened are likely to have a better outcome from the disease process for reasons other than early detection; for example, they are less likely to smoke and more likely to take exercise. Length bias occurs because intermittent screening tests tend to pick up indolent disease that is more likely to have a good prognosis than aggressive disease, which is more likely to be symptomatic and present between screening intervals. Lead-time bias is a product of early diagnosis itself; early diagnosis inevitably leads to an apparently improved duration of survival by shifting the point of diagnosis forward in time so that screening appears to prolong survival without having a real effect on the time course of the disease. To allow for these biases, population-based randomized trials are necessary. In these trials the group randomized to screening must be analyzed as a whole, *including* those who develop interval cancers (cancers that present with symptoms after a negative screening test) and those who do not participate in the screening process. This group must then be compared with a randomly selected control group that is not offered screening and only if a significant improvement in disease-specific mortality is observed in the test group can the screening process be deemed beneficial.

Conclusion

There is high quality evidence that early detection of colorectal cancer by screening reduces colorectal cancer mortality and that detection of adenomas reduces the incidence of colorectal cancer. Currently, the most commonly used screening modality is FOBT, and gFOBT has been supplanted by FIT. Sigmoidoscopy and colonoscopy are clearly effective, but can only really be used on an individual basis as both uptake and costs are likely to prohibit its widespread use in population screening. Current research is focusing on developing new sensitive and specific tests that will be both safe, less invasive and more acceptable to the population, and on examining methods for increasing compliance to screening.

Surveillance for Colorectal Cancer

Principles of Surveillance

After treatment for colorectal cancer with a curative intent, follow-up should be performed for early detection and treatment of eventual local recurrence and metachronous metastatic disease (with the aim to reduce colorectal cancer-related mortality), and for early detection of a subsequent (metachronous) colorectal cancer and/or precancerous lesions (to reduce the incidence of colorectal cancer in patients with potentially increased susceptibility to colorectal cancer) (Rutter et al. 2020). Analysis of 1994–2003 data from nine SEER registries revealed that patients treated for stage II colon cancer have an annual incidence of recurrence ranging between 3.5 to 4%, and those with stage II rectal cancer between 4.5 to 6.4%. This annual recurrence rate rises up to 11% for stage III colorectal cancer (Kunst et al. 2020). Regarding distant metastatic disease, the incidence of metachronous liver metastases and metachronous peritoneal carcinomatosis are 10.3% and 4.2% respectively (Engstrand et al. 2018; Segelman et al. 2012). Most recurrences occur during the first three years of follow-up, and a small proportion occur between year three and year five. Recurrence detected more than five years after curative treatment is possible but has a low incidence (Seo et al. 2013). Therefore, it is commonly agreed that follow-up should be performed during the first three to five years after curative treatment for colon cancer (Argiles et al. 2020). Of note, the National Institute for Health and Care Excellence (NICE) recommends performing follow-up for detection of local recurrence and/or distant metastases for the first three years after potentially curative resection of non-metastatic colorectal cancer ((NICE) 2020).

Surveillance protocols aim at identifying local recurrence and metachronous distant metastases and colorectal neoplasia, and should therefore include endoscopy and imaging techniques, according to the risk of recurrence presented by the patient. This risk is usually estimated based on the UICC TNM stage of the index cancer, but may depend on other factors, notably in rectal cancer (such as CRM status, EMVI and others). There is GRADE IA recommendation for performing surveillance in patients with stage II or III colorectal cancer who underwent resection with curative intent, and GRADE IC in those with stage IV colorectal cancer who underwent treatment with curative intent. In patients with stage I colorectal cancer, there is GRADE IIC evidence that surveillance should be reserved to selected patients (those presenting with high-risk features on histology or those who benefited from local excision rather than proctectomy for rectal cancer) (Hardiman et al. 2021). Surveillance protocols for colorectal cancer are almost invariably based on imaging of the chest and the abdomen, and on endoscopy. However, evidence is growing that patients with T4 colorectal cancer may also benefit from laparoscopy for early detection of metachronous peritoneal carcinomatosis (M1c) (Bastiaenen et al. 2019).

The intervals at which performing the different surveillance modalities have been investigated by several trials. There is evidence that high-intensity surveillance protocol allows earlier detection of local and distant recurrence of colorectal cancer when compared to low-intensity surveillance protocol which, however, does not translate into improved overall survival (Rosati et al. 2016).

Of note, 42% of recurrence are identified outside of medical visits defined by surveillance protocols. Most of these patients are symptomatic, which means that diagnostic measures should be prompted in patients who develop symptoms after colorectal cancer resection (Duineveld et al. 2016).

Existing Surveillance Protocols

There is currently no global consensus on the intervals at which surveillance should be performed. As highlighted by the European Society for Coloproctology (ESCP), national guidelines for follow-up are heterogeneous (Bastiaenen et al. 2019) and depend on professional societies.

Regarding colon cancer, the European Society of Medical Oncology (ESMO) recommends performing physical examination and CEA level every 3–6 months for the first three years, and every six months thereafter until year five. Colonoscopy should be done at year one, and every 3–5 years thereafter. CT of the chest, abdomen and pelvis should be performed every 6–12 months for the first three years for patients at higher risk (Argiles et al. 2020), who are usually defined as patients above UICC stage I.

The Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the British Society of Gastroenterology (BSG) recommend performing colonoscopy 1 year after curative treatment for colorectal cancer. A second colonoscopy can be performed 3 years later if the patient has a life expectancy >10 years and is younger than 75 years old (Rutter et al. 2020). At least two CT scans of the chest, abdomen and pelvis should be performed during the first three years. CEA level every six months for the first three years can be added (Leong et al. 2017). The duration of this follow-up is also supported by the NICE guideline NG151 for colorectal cancer ((NICE) 2020). The American Society of Colon and Rectal Surgeons (ASCRS) recommends performing physical examination and CEA level every 3–6 months for the first two years, and every six months for three additional years. Colonoscopy should be done at year one, and repeated three years later for patients without adenoma and a year later for patients with adenoma(s). CT of the chest, abdomen and pelvis should be performed annually for the first five years (Hardiman et al. 2021).

Regarding rectal cancer, the European Society of Medical Oncology (ESMO) recommends performing physical examination every six months for the first two years, and CEA level every six months for the first three years. Colonoscopy should be done within year one if not done pre-operatively, and every five years thereafter until age 75. At least two CT scans of the chest, abdomen and pelvis should be performed during the first three years. A more intensive protocol is recommended for patients at higher risk for recurrence, notably those who were CRM+. The use of pelvic MRI is recommended but not detailed (Glynne-Jones et al. 2017).

As for colon cancer, the ACPGBI recommends performing colonoscopy at one year and at year four (Rutter et al. 2020). A least two CT scans of the chest, abdomen and pelvis should be performed during the first three years. CEA level every six months for the first three years can be added (Leong et al. 2017).

The ASCRS recommends performing physical examination and CEA level every 3–6 months for the first two years, and every six months for three additional years. Colonoscopy should be done at year one, and repeated three years later for patients without adenoma and a year later for patients with adenoma(s). CT of the chest, abdomen and pelvis should be performed annually for the first five years. Proctoscopy should be done every 6–12 months for 3–5 years for patients who underwent a resection with anastomosis, and every six months for those who had local excision (Hardiman et al. 2021). Despite the evidence that pelvic MRI could constitute a useful addition to CT for the surveillance of rectal cancer, there is no specific recommendation from the main professional societies regarding MRI use in this setting (Lee et al. 2020).

PET-CT is not routinely used for surveillance and should be performed on a case-by-case basis.

Patients who are at higher risk for recurrence, notably those suffering from hereditary colorectal cancer syndrome or inflammatory bowel disease, should be managed with intensive follow-up protocols (Monahan et al. 2020). For instance, there is an 1–4-fold increased risk of colorectal cancer in patients suffering from Crohn's disease (Olen et al. 2020a), and a 1.7-fold increased risk in patients with ulcerative colitis (Olen et al. 2020b), when compared to the reference population. These patients can be further subclassified into risk categories based on the phenotypic expression and activity of the disease and on the familial history for colorectal cancer. The NICE guideline 118 recommends that patients with inflammatory bowel disease but at lower risk for colorectal cancer should be offered colonoscopy at five years after the index diagnosis, those at intermediate risk, at three years, and those at higher risk, at one year ((NICE) 2022). After surgery for inflammatory bowel disease, notably ileoanal pouch surgery, the frequency and methods of surveillance may vary. Also, it should be noted that surveillance in these vulnerable patients often suffers from heterogeneity and that may even not be performed (Samaan et al. 2019). In patients with hereditary colorectal cancer, surveillance depends on the type of mutation(s) identified and on the penetrance of the disease, and several surveillance protocols exist, among which the guidelines from the European Society of Medical Oncology (Stjepanovic et al. 2019).

Prevention of Colorectal Cancer

Introduction

Both hereditary and environmental factors play a role in the pathogenesis of colorectal cancer. Some of the environmental factors are reversible, and can constitute targets for interventions aimed at reducing the incidence of colorectal cancer. Moreover, anti-inflammatory drugs and other molecules were shown to reduce the risk of precursors lesions and colorectal cancer in low-risk patients and in patients with hereditary syndromes predisposing to colorectal cancer, and could play a prophylactic role in specific populations.

Control of Risk Factors

The last century has seen a significant proportion of the world population to experience industrialization, adopt sedentary lifestyle and a diet rich in red meats and processed food, which are risk factors for colorectal cancer (Keum and Giovannucci 2019). The economic development of populations with low human development index has been paralleled by an increase in the incidence of colorectal cancer (Center et al. 2009; Keum and Giovannucci 2019). This increase in the incidence of colorectal cancer has also demonstrated in populations migrating from low risk areas to high risk areas (Mousavi et al. 2012). It has been estimated that the population attributable fractions (PAF) for bowel cancer is of 54.1%, meaning that 54.1% of cases of bowel cancer are attributed to known risk factors (Brown et al. 2018).

So far, obesity, western dietary pattern, processed meat, red meat, alcohol, and smoking have been identified as risk factors for colorectal cancer, whereas physical activity, prudent dietary pattern, fiber intake, whole grain intake, and total calcium intake were identified as protective factors against colorectal cancer (Keum and Giovannucci 2019; Park et al. 2017). The microbiome is also likely to play a potential role (Saus et al. 2019; Vigneswaran and Shogan 2020).Therefore, public health interventions should aim at reducing the risk factors for colorectal cancer and promote the adoption of protective factors.

Several professional societies have produced recommendations for preventing colorectal cancer. For instance, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) recommends that patients should limit the consumption of red meat, processed meat, and refined carbohydrates, and should observe a low carbohydrate diet. Moreover, after treatment for colorectal cancer, patients should be encouraged to undergo increased physical activity and follow weight management diet (Leong et al. 2017). The World Health Organization (WHO) Collaborating Center for the Prevention of Colorectal Cancer recommends to limit fat consumption to 20% of total calories, to have a balanced diet with 5–8 servings of fruits, vegetables and cereals, comprising at least 25g of daily fiber, to avoid excess calories and being overweight, to avoid tobacco, minimize alcohol intake, and to exercise daily (Winawer et al. 1995).

Chemoprophylaxis

Evidence cumulated over the last 20 years indicates that nonsteroidal anti-inflammatory drugs allow prevention of precursor lesions and of colorectal cancer (Drew et al. 2016).

Randomized controlled trials showed that the daily use of aspirin decreases the incidence of recurrent colorectal adenomas when compared to placebo in patients with a history of adenomas (Baron et al. 2003) or a history of colorectal cancer (Sandler et al. 2003). In the longer term, the prospective follow-up of 135,965 healthcare professionals of the Nurses' Health Study and the Health Professionals Follow-up Study demonstrated that regular use of aspirin decreased the risk of overall cancer (RR: 0.97, 95% CI: 0.94–0.99) and colorectal cancer (RR: 0.81, 95%CI: 0.75–0.88). Of note, the beneficial preventive effect was significant when using 0.5–1.5 tablet per week for at least 6 years (Cao et al. 2016). Analysis of two large randomized trials with follow-up of more than 20 years showed that aspirin decreases the risk of colorectal cancer (HR: 0.74, 95% CI: 0.56–0.97), but the effect was only found after a latency of 10 years and was the highest if aspirin was taken for 5 years or more (Flossmann and Rothwell 2007). This preventive effect was also shown for other non-steroidal anti-inflammatory drugs. For instance, the daily use of 400mg celecoxib decreased the 3-year incidence of recurrent adenomas when compared to placebo (RR: 0.64, 95% CI: 0.56–0.75) (Arber et al. 2006).

Similar evidence can be transposed to patients with the risk of hereditary colorectal cancer. In patients with familial adenomatosis polyposis (FAP), aspirin (Ishikawa et al. 2021), sulindac (Giardiello et al. 2002; Samadder et al. 2018), celecoxib (Steinbach et al. 2000) and Omega-3 polyunsaturated fatty acids (West et al. 2010) have been shown to reduce the polyp load and/or size. In patients with HNPCC, daily 600 mg aspirin was shown to reduce the incidence of HNPCC-associated cancers (Burn et al. 2011). Currently, daily aspirin intake for more than two years is recommended by the National Institute of Health and Care Excellence (NICE) for reducing the risk of colorectal cancer in patients with Lynch Syndrome ((NICE) 2020).

Moreover, the US Preventive Services Task Force (USPSTF) recommends low-dose aspirin for the primary prevention of colorectal cancer in patients aged 50 to 59 years and who have a life expectancy greater than 10 years. For other populations, the benefits have to be weighted with the risks of such treatment (including gastrointestinal bleeding and cerebrovascular accident), and no recommendation has been made so far.

Key Take Home Messages

There is high quality evidence that early detection of colorectal cancer by screening reduces colorectal cancer mortality and that detection of adenomas reduces the incidence of colorectal cancer. Currently, the most commonly used screening modality is FOBT, and gFOBT has been supplanted by FIT. Sigmoidoscopy and colonoscopy are clearly effective, but can only really be used on an individual basis as both uptake and costs are likely to prohibit its widespread use in population screening. Currently research is focusing on developing new sensitive and specific tests that will be both safe, less invasive and more acceptable to the population, and on examining methods for increasing compliance to screening.

Surveillance after treatment for colorectal cancer allows early identification of localized and/or distant recurrence and optimal treatment of these recurrences. Moreover, colonoscopic surveillance allows removal of precancerous lesions (adenomas) in patients who are at higher risk for colorectal cancer. Surveillance should follow local guidelines and/or guidelines released by professional societies in the field.

Prevention of colorectal cancer relies mostly on the control of modifiable risk factors for colorectal cancer, which should be promoted by public health campaigns and by primary care physicians. In selected patients at higher risk, non-steroidal anti-inflammatory drugs reduce the risk of colorectal cancer.

Areas for Further Research

In terms of prevention of colorectal cancer, future areas to explore include the role of the microbiome on the development of colorectal cancer, the mechanistic of the interplay between risk factor for colorectal cancer (Lawler et al. 2018), the effect of modulation of the microbiome on the incidence of colorectal cancer, and the identification of populations who may benefit from chemoprophylaxis. In terms of screening, future research is needed to identify methods allowing increasing compliance to screening programs, to document the effect on long-term mortality and colorectal cancer incidence of different screening modalities, and to better identify high-risk patients at the population level (Kanth and Inadomi 2021). In terms of surveillance, future research is needed to determine the effect of surveillance protocols on long-term colorectal cancer incidence and mortality, to define the surveillance modalities in patients outside the age for screening (young patients and patients older than 75), to assess novel and alternative methods for screening, and on tailoring the modalities of surveillance protocols according to the personal risk presented by the patient (taking into account phenotypic and genetic factors of the disease) (Rutter et al. 2020).

Trusted Websites for Further Reading

https://www.gov.uk/government/publications/health-matters-preventing-bowel-cancer/health-matters-improving-the-prevention-and-detection-of-bowel-cancer

https://www.nice.org.uk/guidance/NG151

https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/colorectal-cancer-screening-guidelines.html

References

Ahmed, S., Leslie, A., Thaha, M.A. et al. (2005). Lower gastrointestinal symptoms are not predictive of colorectal neoplasia in a faecal occult blood screen-positive population. *Br J Surg* 92: 478–481.

Ait Ouakrim, D., Pizot, C., Boniol, M. et al. (2015). Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. *BMJ* 351: h4970.

Arber, N., Eagle, C.J., Spicak, J. et al. (2006). Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 355: 885–895.

Argiles, G., Tabernero, J., Labianca, R. et al. (2020). Localised colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 31: 1291–1305.

Atkin, W., Wooldrage, K., Parkin, D.M. et al. (2017). Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 389: 1299–1311.

Atkin, W.S., Edwards, R., Kralj-Hans, I. et al. (2010). Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 375: 1624–1633.

Atkin, W.S., Edwards, R., Wardle, J. et al. (2001). Design of a multicentre randomised trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. *J Med Screen* 8: 137–144.

Baron, J.A., Cole, B.F., Sandler, R.S. et al. (2003). A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 348: 891–899.

Bastiaenen, V.P., Hovdenak Jakobsen, I., Labianca, R. et al. (2019). Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology. *Colorectal Dis* 21: 392–416.

Bastiaenen, V.P., Klaver, C.E.L., Kok, N.F.M. et al. (2019). Second and third look laparoscopy in pT4 colon cancer patients for early detection of peritoneal metastases; the COLOPEC 2 randomized multicentre trial. *BMC Cancer* 19: 254.

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68: 394–424.

Bretthauer, M., Kaminski, M.F., Loberg, M. et al. (2016). Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med* 176: 894–902.

Brown, K.F., Rumgay, H., Dunlop, C. et al. (2018). The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer* 118: 1130–1141.

Burn, J., Gerdes, A.M., Macrae, F. et al. (2011). Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 378: 2081–2087.

Buskermolen, M., Cenin, D.R., Helsingen, L.M. et al. (2019). Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. *BMJ* 367: l5383.

Cao, Y., Nishihara, R., Wu, K. et al. (2016). Population-wide impact of Long-term use of aspirin and the risk for cancer. *JAMA Oncol* 2: 762–769.

Center, M.M., Jemal, A., and Ward, E. (2009). International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 18: 1688–1694.

Chiu, H.M., Jen, G.H., Wang, Y.W. et al. (2021). Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. *Gut* 70: 2321–2329.

Committee UNS. (2018). Bowel cancer. Adult screening programme. https://view-health-screening-recommendations.service.gov.uk/bowel-cancer.

D'Souza, N., Georgiou Delisle, T., Chen, M. et al. (2021). Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. *Gut* 70: 1130–1138.

Dekker, E., Tanis, P.J., Vleugels, J.L.A. et al. (2019). Colorectal cancer. *Lancet* 394: 1467–1480.

Dobrow, M.J., Hagens, V., Chafe, R. et al. (2018). Consolidated principles for screening based on a systematic review and consensus process. *CMAJ* 190: E422–E429.

Drew, D.A., Cao, Y., and Chan, A.T. (2016). Aspirin and colorectal cancer: the promise of precision chemoprevention. *Nat Rev Cancer* 16: 173–186.

Duineveld, L.A., van Asselt, K.M., Bemelman, W.A. et al. (2016). Symptomatic and asymptomatic colon cancer recurrence: a multicenter cohort study. *Ann Fam Med* 14: 215–220.

Engstrand, J., Nilsson, H., Stromberg, C. et al. (2018). Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC Cancer* 18: 78.

Faivre, J., Dancourt, V., Lejeune, C. et al. (2004). Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 126: 1674–1680.

Flossmann, E., Rothwell, P.M., British Doctors Aspirin T et al. (2007). Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 369: 1603–1613.

Garcia-Albeniz, X., Hsu, J., Bretthauer, M. et al. (2017). Effectiveness of screening colonoscopy to prevent colorectal cancer among medicare beneficiaries aged 70 to 79 years: a prospective observational study. *Ann Intern Med* 166: 18–26.

Gavin, D.R., Valori, R.M., Anderson, J.T. et al. (2013). The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK. *Gut* 62: 242–249.

Giardiello, F.M., Yang, V.W., Hylind, L.M. et al. (2002). Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 346: 1054–1059.

Glynne-Jones, R., Wyrwicz, L., Tiret, E. et al. (2017). Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 28: iv22–iv40.

Grobbee, E.J., van der Vlugt, M., van Vuuren, A.J. et al. (2020). Diagnostic yield of one-time colonoscopy vs one-time flexible sigmoidoscopy vs multiple rounds of mailed fecal immunohistochemical tests in colorectal cancer screening. *Clin Gastroenterol Hepatol* 18: 667–675 e1.

Guittet, L., Bouvier, V., Mariotte, N. et al. (2007). Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut* 56: 210–214.

Hamilton, W., Lancashire, R., Sharp, D. et al. (2009). The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study. *BMC Med* 7: 17.

Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H. et al. (1996). Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 348: 1472–1477.

Hardiman, K.M., Felder, S.I., Friedman, G. et al. (2021). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the surveillance and survivorship care of patients after curative treatment of colon and rectal cancer. *Dis Colon Rectum* 64: 517–533.

Helsingen, L.M., Vandvik, P.O., Jodal, H.C. et al. (2019). Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline. *BMJ* 367: l5515.

Herrero, J.M., Vega, P., Salve, M. et al. (2018). Symptom or faecal immunochemical test based referral criteria for colorectal cancer detection in symptomatic patients: a diagnostic tests study. *BMC Gastroenterol* 18: 155.

Hoffman, R.M., Levy, B.T., and Allison, J.E. (2021). Rising use of multitarget stool DNA testing for colorectal cancer. *JAMA Netw Open* 4: e2122328.

Holme, O., Loberg, M., Kalager, M. et al. (2014). Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA* 312: 606–615.

Hull, M.A., Rees, C.J., Sharp, L. et al. (2020). A risk-stratified approach to colorectal cancer prevention and diagnosis. *Nat Rev Gastroenterol Hepatol* 17: 773–780.

Imperiale, T.F., Ransohoff, D.F., Itzkowitz, S.H. et al. (2014). Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 370: 1287–1297.

Ishikawa, H., Mutoh, M., Sato, Y. et al. (2021). Chemoprevention with low-dose aspirin, mesalazine, or both in patients with familial adenomatous polyposis without previous colectomy (J-FAPP Study IV): a multicentre, double-blind, randomised, two-by-two factorial design trial. *Lancet Gastroenterol Hepatol* 6: 474–481.

Islami, F., Ward, E.M., Sung, H. et al. (2021). Annual report to the nation on the status of cancer, part 1: national cancer statistics. *J Natl Cancer Inst*.

Jeon, J., Du, M., Schoen, R.E. et al. (2018). Determining risk of colorectal cancer and starting age of screening based on lifestyle, environmental, and genetic factors. *Gastroenterology* 154: 2152–2164 e19.

Jorgensen, O.D., Kronborg, O., and Fenger, C. (2002). A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut* 50: 29–32.

Kanth, P. and Inadomi, J.M. (2021). Screening and prevention of colorectal cancer. *BMJ* 374: n1855.

Katsoula, A., Paschos, P., Haidich, A.B. et al. (2017). Diagnostic accuracy of fecal immunochemical test in patients at increased risk for colorectal cancer: a meta-analysis. *JAMA Intern Med* 177: 1110–1118.

Keum, N. and Giovannucci, E. (2019). Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol* 16: 713–732.

Kewenter, J., Brevinge, H., Engaras, B. et al. (1994). Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. *Scand J Gastroenterol* 29: 468–473.

Kim, S.Y., Kim, H.S., and Park, H.J. (2019). Adverse events related to colonoscopy: global trends and future challenges. *World J Gastroenterol* 25: 190–204.

Kunst, N., Alarid-Escudero, F., Aas, E. et al. (2020). Estimating population-based recurrence rates of colorectal cancer over time in the United States. *Cancer Epidemiol Biomarkers Prev* 29: 2710–2718.

Ladabaum, U. and Comparative Effectiveness, M.A. (2016). Cost effectiveness of a multitarget stool DNA test to screen for colorectal Neoplasia. *Gastroenterology* 151: 427–439 e6.

Lawler, M., Alsina, D., Adams, R.A. et al. (2018). Critical research gaps and recommendations to inform research prioritisation for more effective prevention and improved outcomes in colorectal cancer. *Gut* 67: 179–193.

Lee, S.L., Shin, Y.R., and Kim, K. (2020). The added value of pelvic surveillance by MRI during postoperative follow-up of rectal cancer, with a focus on abbreviated MRI. *Eur Radiol* 30: 3113–3124.

Leong, K., Hartley, J., and Karandikar, S. (2017). Association of Coloproctology of Great Britain & Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017) - follow up, lifestyle and survivorship. *Colorectal Dis* 19 (Suppl 1): 67–70.

Lin, J.S., Perdue, L.A., Henrikson, N.B. et al. (2021). Screening for colorectal cancer: updated evidence report and systematic review for the US preventive services task force. *JAMA* 325: 1978–1998.

Malila, N., Oivanen, T., Malminiemi, O. et al. (2008). Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design. *BMJ* 337: a2261.

Mandel, J.S., Bond, J.H., Church, T.R. et al. (1993). Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota colon cancer control study. *N Engl J Med* 328: 1365–1371.

Mandel, J.S., Church, T.R., Bond, J.H. et al. (2000). The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 343: 1603–1607.

Marshall, T., Lancashire, R., Sharp, D. et al. (2011). The diagnostic performance of scoring systems to identify symptomatic colorectal cancer compared to current referral guidance. *Gut* 60: 1242–1248.

Miller, E.A., Pinsky, P.F., Schoen, R.E. et al. (2019). Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. *Lancet Gastroenterol Hepatol* 4: 101–110.

Monahan, K.J., Bradshaw, N., Dolwani, S. et al. (2020). Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut* 69: 411–444.

Mousavi, S.M., Fallah, M., Sundquist, K. et al. (2012). Age- and time-dependent changes in cancer incidence among immigrants to Sweden: colorectal, lung, breast and prostate cancers. *Int J Cancer* 131: E122–8.

(NICE). (2020). Colorectal cancer: NICE guideline (NG151).

(NICE). (2022 September 20). Guideline 118: colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas.

Olen, O., Erichsen, R., Sachs, M.C. et al. (2020a). Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. *Lancet Gastroenterol Hepatol*. Online.

Olen, O., Erichsen, R., Sachs, M.C. et al. (2020b). Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. *Lancet* 395: 123–131.

Park, S.Y., Boushey, C.J., Wilkens, L.R. et al. (2017). High-quality diets associate with reduced risk of colorectal cancer: analyses of diet quality indexes in the multiethnic cohort. *Gastroenterology* 153: 386–394 e2.

Pickhardt, P.J., Choi, J.R., Hwang, I. et al. (2003). Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 349: 2191–2200.

Pignone, M., Campbell, M.K., Carr, C. et al. (2001). Meta-analysis of dietary restriction during fecal occult blood testing. *Eff Clin Pract* 4: 150–156.

Plumb, A.A., Halligan, S., Nickerson, C. et al. (2014). Use of CT colonography in the English Bowel Cancer Screening Programme. *Gut* 63: 964–973.

Potter, N.T., Hurban, P., White, M.N. et al. (2014). Validation of a real-time PCR-based qualitative assay for the detection of methylated SEPT9 DNA in human plasma. *Clin Chem* 60: 1183–1191.

Rex, D.K., Cutler, C.S., Lemmel, G.T. et al. (1997). Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 112: 24–28.

Rex, D.K., Johnson, D.A., Anderson, J.C. et al. (2009). American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 104: 739–750.

Rosati, G., Ambrosini, G., Barni, S. et al. (2016). A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Ann Oncol* 27: 274–280.

Rutter, M.D., East, J., Rees, C.J. et al. (2020). British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 69: 201–223.

Samaan, M.A., Forsyth, K., Segal, J.P. et al. (2019). Current practices in ileal pouch surveillance for patients with ulcerative colitis: a multinational, retrospective cohort study. *J Crohns Colitis* 13: 735–743.

Samadder, N.J., Kuwada, S.K., Boucher, K.M. et al. (2018). Association of sulindac and erlotinib vs placebo with colorectal neoplasia in familial adenomatous polyposis: secondary analysis of a randomized clinical trial. *JAMA Oncol* 4: 671–677.

Sandler, R.S., Halabi, S., Baron, J.A. et al. (2003). A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 348: 883–890.

Saus, E., Iraola-Guzman, S., Willis, J.R. et al. (2019). Microbiome and colorectal cancer: roles in carcinogenesis and clinical potential. *Mol Aspects Med* 69: 93–106.

Scholefield, J.H., Moss, S., Sufi, F. et al. (2002). Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 50: 840–844.

Scholefield, J.H., Robinson, M.H., Mangham, C.M. et al. (1998). Screening for colorectal cancer reduces emergency admissions. *Eur J Surg Oncol* 24: 47–50.

Segelman, J., Granath, F., Holm, T. et al. (2012). Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 99: 699–705.

Segnan, N., Armaroli, P., Bonelli, L. et al. (2011). Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian randomized controlled Trial–SCORE. *J Natl Cancer Inst* 103: 1310–1322.

Seo, S.I., Lim, S.B., Yoon, Y.S. et al. (2013). Comparison of recurrence patterns between</=5 years and > 5 years after curative operations in colorectal cancer patients. *J Surg Oncol* 108: 9–13.

Shapiro, J.A., Bobo, J.K., Church, T.R. et al. (2017). A comparison of fecal immunochemical and high-sensitivity guaiac tests for colorectal cancer screening. *Am J Gastroenterol* 112: 1728–1735.

Shaukat, A. and Levin, T.R. (2022). Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol* 19: 521–531. https://doi.org/10.1038/s41575-022-00612-y.

Steinbach, G., Lynch, P.M., Phillips, R.K. et al. (2000). The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 342: 1946–1952.

Stjepanovic, N., Moreira, L., Carneiro, F. et al. (2019). Hereditary gastrointestinal cancers: ESMO clinical practice guidelines for diagnosis, treatment and follow-updagger. *Ann Oncol* 30: 1558–1571.

Stoop, E.M., de Haan, M.C., de Wijkerslooth, T.R. et al. (2012). Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol* 13: 55–64.

Uspst, F., Kw, D., MJ, B. et al. (2021). Screening for colorectal cancer: US preventive services task force recommendation statement. *JAMA* 325: 1965–1977.

van Rossum, L.G., van Rijn, A.F., Laheij, R.J. et al. (2008). Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 135: 82–90.

Verne, J.E., Aubrey, R., Love, S.B. et al. (1998). Population based randomized study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing. *BMJ* 317: 182–185.

Vigneswaran, J. and Shogan, B.D. (2020). The role of the intestinal microbiome on colorectal cancer pathogenesis and its recurrence following surgery. *J Gastrointest Surg* 24: 2349–2356.

West, N.J., Clark, S.K., Phillips, R.K. et al. (2010). Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 59: 918–925.

(WHO) WHO. (2019). Digestive system tumours.

Wilson, J.M.G., Jungner, G., and Organization, WH (1968). *Principles and Practice of Screening for Disease*. World Health Organization.

Winawer, S.J., St John, D.J., Bond, J.H. et al. (1995). Prevention of colorectal cancer: guidelines based on new data. WHO collaborating center for the prevention of colorectal cancer. *Bull World Health Organ* 73: 7–10.

Wong, C.K., Fedorak, R.N., Prosser, C.I. et al. (2012). The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer. *Int J Colorectal Dis* 27: 1657–1664.

National Cancer Institute. (2022). National cancer institute: surveillance E, and end results program. *Cancer Stat Facts: Colorectal Cancer*.

12 Colorectal Cancer

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Clinical Presentation and Case Scenarios

Jeremy Meyer & Justin Davies

Introduction

The objective of this section of the book is to highlight the importance of multidisciplinary input in looking after patients with colorectal cancer, from the gastro-enterologists, pathologists, and radiologists who provide the diagnosis and staging; the surgeons who remove the tumor with adequate lymphadenectomy or provide palliative surgery to improve quality of life, the oncologists who may administer chemotherapy and/or radiotherapy to decrease the likehood of recurrence and improve survival, and finally the clinical nurse specialists and stoma nurses who provide the central integral role of coordinating the patient pathway, counselling, and advice and support about stoma and other care.

Patients with colorectal cancer can present with a myriad of symptoms and signs to different health professionals, including general practitioners, emergency physicians, gastro-enterologists, and other hospital specialists, as well as specialist nurses. Therefore, it is important that anyone who may come into contact with such patients should be able to recognize the common presentation patterns.

By studying the case scenarios given below, you will become familiar with the usual clinical presentations of patients with colorectal cancer, as well as with the diagnostic and therapeutic managements adopted in different situations. A number of questions will be asked at the end of each case. You may not be able to answer these until you have read the rest of this chapter about the multidisciplinary approach to colorectal cancer. However, once you have read these sections, you should be able to answer all of the questions fully. In the final section you will find the detailed answers to the clinical cases scenarios.

Case 1

A 62-year-old man presents with a 3-month history of tiredness and occasional rectal bleeding. Clinical examination, including digital rectal examination, is normal. Investigations reveal a hypochromic microcytic anemia consistent with iron-deficiency, and serum ferritin is confirmed to be low. Colonoscopy finds a lesion in the caecum and biopsies confirm adenocarcinoma. A computed tomography (CT) of the chest and the abdomen does not identify any distant metastases but stages the lesion as being cT3 N+. The patient undergoes a right hemicolectomy. Histologic analysis reveals a pT3 N2 poorly differentiated adenocarcinoma of the colon. There is no microsatellite instability. Adjuvant chemotherapy is proposed to the patient.

Questions

1 What are the routine staging modalities for colon cancer?
2 What surgical approach should be preferentially used?
3 What adjuvant chemotherapy regimen should be offered to this patient after surgery?
4 What follow-up should be performed?

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Case 2

A 32-year-old man presents with occasional rectal bleeding. Flexible sigmoidoscopy, completed by colonoscopy, shows over 100 polyps in the entire colon. CT does not identify any cancer, suspicious lymph node, or distant metastases. Gastroscopy does not identify any lesion in the upper gastrointestinal tract. Genetic testing finds a mutation of the APC gene on codon 1309. The patient is offered prophylactic surgery, and benefits from a laparoscopic proctocolectomy with creation of an ileo-anal pouch. A protection loop ileostomy is closed after three months.

Questions

1 What are the surgical options in patients with mutation in the APC gene?
2 What should be the follow-up after (procto)-colectomy for familial adenomatous polyposis (FAP)?
3 What is the evidence regarding chemoprophylaxis of polyps in patients with FAP?

Case 3

A 49-year-old woman attends her general practitioner with symptoms of respiratory tract infection. Blood tests shows a moderate inflammatory syndrome and a microcytic anemia. Additional history picks up a change in bowel habit for a few months. The brother of the patient was diagnosed with colorectal cancer before the age of 50 years, and her mother passed away due to endometrial cancer. After resolution of the respiratory tract infection, the patient undergoes a colonoscopy, which shows a sigmoid cancer, located at 25 cm from the anal verge, with histology positive for adenocarcinoma. CT demonstrates a cT3 mid sigmoid cancer without any distant metastasis. The patient has surgery in the form of a high anterior resection. Pathology of the operative specimen is pT3 N0 V0. Micro-satellite instability (MSI)-high is identified by PCR. Immunohistochemistry shows a loss in mismatch repair (MMR) protein coded by gene MLH1. Additional testing does not find any mutation in BRAF or hypermethylation of the MLH1 promoter, therefore excluding a sporadic colorectal cancer with MSI. Mutation of the gene is then confirmed on chromosome 3p21.3. Genetic testing of the 21-year-old daughter of the patient identifies a similar mutation. The patient is put under surveillance, but six months later she complains of vaginal bleeding. A retrospective analysis of the index CT report finds in the detailed description a mention of increased endometrial thickness.

Questions

1 What are the clinical criteria used to screen for individuals susceptible to Lynch syndrome?
2 If Lynch syndrome is clinically suspected, what should be the diagnostic work-up?
3 What would have been the optimal management of this patient?
4 What chemotherapy regimen could have been proposed if the pathology of the operative specimen was pT4 N0 V1?
5 What follow-up should be proposed to the daughter of the patient?

Case 4

A 49-year-old man presents with a 6-month history of change in bowel habit. His general practitioner requests a colonoscopy, which shows a 3 cm lesion in the mid rectum, which is classified as Paris 0-IIa. The gastroenterologist performs a biopsy which shows high-grade dysplasia. A CT does not find any distant metastases. A pelvic MRI describes the lesion as being posterior, located at 6 cm from the anal verge, and of stage mrT1/2 V0 N0 MRF clear. No endoanal ultrasound is available. Repeat biopsy shows again some high-grade dysplasia. The patient benefits from a local excision using a transanal minimally invasive surgery (TAMIS) approach with full-thickness dissection. Pathology shows a pT1sm1 LV- R0 adenocarcinoma.

Questions

1 What is the definition of early rectal cancer?
2 What would be the best TAMIS approach?
3 Would the treatment be different if the cancer was pT1 (sm2) V1?
4 What is the place of (neo)adjuvant treatment in this scenario?

Case 5

A 68-year-old obese man, with a body mass index of 45 kg/m^2, presents with a one-month history of rectal bleeding, tenesmus, and altered bowel habit. On examination, he has a firm mid-rectal tumor. Endoscopy does not identify any other lesion and confirms the presence of poorly differentiated adenocarcinoma. CT does not show any distant metastasis. MRI of the pelvis describes a mrT3N1 mid rectal tumor with a threatened mesorectal fascia (MRF+), located at 6 cm from the anal verge and at least at 1.5 cm from the levator ani. The patient undergoes long-course neo-adjuvant radio-chemotherapy, composed of 45 Gy in 25 fractions and synchronous capecitabine. Restaging MRI reveals significant reduction of the tumor mass (partial response). The patient subsequently undergoes a low anterior resection. Histology reveals an ypT2 N0 adenocarcinoma. Excision margins are clear of tumor.

Questions

1 What should be the preferred surgical approach be in this patient?
2 What is the definition of MRF+ and why is it of importance?
3 Should this patient have been offered radiotherapy alone before surgery?
4 What would be the therapeutic options if the patient had complete clinical response after neoadjuvant treatment?

Case 6

A 56-year-old woman presents to the Emergency Department with rectal bleeding. Her hemoglobin concentration is 79 g/l. Digital rectal examination palpates an indurated posterior lesion, at the level of the sphincters. The lesion seems fixed to the sphincters. The patient undergoes investigation, and colonoscopy identifies a rectal lesion, which is not obstructive, and confirmed to be in the distal rectum. Biopsy is positive for adenocarcinoma. Pelvic MRI describes the lesion to be posterior, 3 to 5 cm from the anal verge, to invade both sphincters and the levator ani on the left side. Also, there are enlarged lymph nodes alongside the left external iliac vessels. CT does not identify any distant metastasis, except these enlarged unilateral external iliac lymph nodes. After discussion at MDT, a PET-CT is performed, and shows hypercaptation at the level of the lateral pelvic lymph nodes. The patient benefits from long-course neo-adjuvant radio-chemotherapy. Restaging by pelvic MRI and PET-CT shows partial shrinkage of the lateral pelvic lymph nodes and partial clinical response of the primary lesion. Partial response of the primary lesion is confirmed by flexible sigmoidoscopy.

Questions

1 What is the prevalence of lateral lymph nodes in low rectal cancer?

2 What would be the therapeutic option for the lateral pelvic lymph nodes?

Endoscopic Management of Colorectal Lesions

Kirill Basiliya & Gareth Corbett

[Aspects of the endoscopic management of gastrointestinal cancer is also in Chapter 4]

Introduction

The beginnings of endoscopy can be traced back to 1805, when Philipp Bozzini published a description of the *Lichtleiter*, a device that enabled light to be channeled into a tube and allowed the inspection of hollow anatomic cavities. This was followed by the development of rigid endoscopes in the nineteenth century and flexible endoscopes in the mid-twentieth century. In 1969 Drs William Wolff and Hiromi Shinya performed the first electrosurgical snare polypectomy, transforming the colonoscopy from a diagnostic to a therapeutic procedure. The introduction of the video endoscope in 1983 allowed the images to be visualized on a monitor instead of an eyepiece. Subsequent innovations have included better maneuverability, improved imaging (including enhanced imaging techniques) and the development of a wide range of dedicated instruments that can be introduced through the working channel. Colonoscopy offers the gold standard in the diagnosis of benign and malignant colorectal lesions. However, there remains a risk of lesions not being detected and the concept of a post colonoscopy colorectal cancer has developed, this being a colorectal cancer detected within two years of an index colonoscopy. This is the most significant diagnostic risk to patients and to allay this risk practice has evolved. Colonoscopy has a suite of metrics for endoscopists in which they can assess their individual quality of practice. In addition, advances in the image resolution of the endoscope equipment combined more recently with artificial intelligence mean that endoscopists find themselves at a time where the risk of a missed cancer is reducing.

Endoscopic techniques providing management of colorectal neoplastic pathology has developed at pace with evolving techniques providing an alternative to surgical intervention. This progression in practice has provided options such as advanced endoscopic resection techniques including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), endoscopic full thickness resection and endoscopically guided insertion of self-expanding metal stents.

Bowel Preparation

Stool in the colon precludes mucosal visualization and it is essential that the colon is sufficiently cleaned prior to the procedure. The cleaner the colon, the more premalignant colonic lesions are detected (Froehlich et al. 2005). The cleanliness of the colon is expressed using the Boston Bowel Preparation Score. In this score, a score of 1 to 3 is given to each of the colonic segments (right, transverse and left-sided colon) with a higher score indicating a cleaner colon. Colonic cleansing is usually achieved using the combination of a diet and a laxative taken before the procedure. Many formulations of colonoscopy preparations exist, but most can be divided into osmotic and stimulants. Osmotic laxatives draw water from the stool and bowel and soften the stool. The most commonly used osmotic laxatives are based on polyethylene glycol formulations. Stimulant laxatives stimulate peristalsis and speed up colonic transit time. Commonly used stimulant laxatives include bisacodyl or sodium picosulfate. Colonoscopy preparation regimens often contain a mixture of an osmotic and stimulant laxative. Laxative side effects are rare but include electrolyte disturbances and dehydration and can adversely affect kidney function in vulnerable individuals. Polyethylene glycol formulations often contain aspartame and ascorbate as adjuvants, and these are contraindicated in patients with phenylketonuria or glucose-6-phosphate dehydrogenase deficiency. Bisacodyl and sodium picosulfate have been associated with rare instances of ischemic colitis.

Endoscopic Imaging Technology

Image Resolution

Advances in charge-coupled device (CCD) chip and monitor resolution have enabled imaging resolution in endoscopy to develop from standard resolution (<400000 pixels/image) to high definition (>800000 pixels/image). Compared to standard resolution the use of high definition in endoscopy has a limited effect on the number of lesions found; a meta-analysis estimated that the incremental yield of high definition endoscopy for the detection of any colon polyp was 3.8%, but there was no difference in the detection of high-risk lesions (Subramanian et al. 2011). Despite the fact that high definition endoscopy does not have a major effect of the number of detected lesions in the colon, the higher resolution does enable a better visualization of the lesion which in theory could enable more precise characterization. Of note, the newest endoscopes support a resolution up to 4K ultra high definition, which implies a fourfold increase in pixel number compared to high definition.

Chromoendoscopy

Application of a dye to the colonic mucosa can be used to highlight focal lesions. The main dye used is diluted indigo-carmine. It is inert and is not absorbed nor does it react with the mucosa, meaning that it has an excellent safety profile. It can be used to focally highlight an area of interest that was identified on white light endoscopy or by spraying dye throughout the colon. Chromoendoscopy does increase the yield of premalignant lesions (Brown et al. 2016) but requires good bowel preparation, can be laborious and extends the duration of colonoscopy.

Narrow Band Imaging

The peak light absorption of hemoglobin occurs in the blue and green color spectrum. This means that hemoglobin (and, by extension, blood vessels) will appear dark when viewed in green and blue light. This is exploited in narrow band imaging (NBI). Illuminating the endoscopic field of vision with 415 nm (blue light) and 540 nm (green light) makes the (micro)vasculature appear dark in contrast with the surrounding tissue. Whether NBI increased polyp detection was subject to an ongoing debate, but a large meta-analysis showed that polyps were detected in 42.3% of participants examined by white light endoscopy and 45.2% when examined with NBI (Atkinson et al. 2019). The added benefit of NBI was most pronounced if bowel preparation was optimal, highlighting the fact that a good bowel preparation is the cornerstone of a successful colonoscopy. NBI has shown good results in differentiating between adenoma and non-adenoma lesions (McGill et al. 2013) which has led to the idea that NBI-assisted imaging could replace a histological examination of the resected lesion. Unfortunately, the largest trial designed to answer this question found that NBI underperformed compared to the histological diagnosis (Rees et al. 2017) suggesting that, at least for now, a histological diagnosis remains indispensable.

Digital Image Enhanced Endoscopy

Digital image enhanced endoscopy describes real-time image processing algorithms that enhance a particular aspect of the image. This can be used to enhance contrast, highlight small uneven areas of the mucosa or increase the contrast between blood vessels and the surrounding mucosa. Theoretical benefits of digital image enhanced endoscopy in contrast with NBI are the lack of illumination that is present in NBI and the benefit of multiple modes of image enhancement. However, the limited data comparing NBI to digital image enhanced endoscopy shows no superiority of either system (Lee et al. 2011). Most major endoscope manufacturers offer some form of digital image enhanced endoscopy; Pentax offers I-Scan, Fujinon Fuji Intelligent Color Enhancement (FICE) and Olympus Texture and color enhancement imaging (TXI). All these algorithms are proprietary and there is little evidence comparing them amongst each other.

Artificial Intelligence

Artificial intelligence (AI), also known as computer-aided detection (CADe) is an area of rapid development in luminal endoscopy. Improvements in computer processing and better algorithms (in particular machine learning) have enabled the development of real-time processing of endoscopic images to identify pre-malignant colonic lesions. Multiple trials (Gong et al. 2020; Repici et al. 2020; Wang et al. 2020) and a systematic review with meta-analysis (Spadaccini et al. 2021) suggest that CADe increases the adenoma detection rate. Another area in which AI could be applied is the characterization of a lesion once it has been identified. Non-randomized studies have suggested that AI can distinguish between adenoma and non-adenoma lesions. It is currently unknown how well AI compares with a human observer or the final pathological diagnosis but studies to answer these questions are ongoing.

Colonoscopy Quality

Colonoscopy is a procedure in which significant variability in quality of practice is observed and with poor quality colonoscopy having an association with increased rates of interval colorectal cancers it is vital that quality can be assessed and monitored. This process starts with training, ensuring that before independent practice is achieved an endoscopist can demonstrate that key performance indicators are met.

The suite of colonoscopy metrics allow an assessment of the overall practice and these metrics interact to allow determination of the quality of that practice (Rees et al. 2016). The key metrics are:

- Caecal intubation rate (the percentage of procedures in which the colonoscope enters the caecum)
- Adenoma detection rate – the percentage of procedures with at least one adenoma diagnosed
- Bowel preparation quality – the percentage of procedures in which the bowel preparation quality provides sufficient cleansing to allow diagnosis

- Rectal retroversion rate – the percentage of procedures in which the endoscope is inverted in the rectum to visualize the anorectal margin
- Colonoscope withdrawal time – the amount of time the endoscopist takes to withdraw the colonoscopy while observing the colonic mucosa
- Use of sedation – a safety measure of sedation dosing in different age groups to ensure sedation is used safely
- Number of colonoscopy procedures undertaken per annum
- Comfort during colonoscopy – a five-point scale in which the comfort of the patient during a consciously sedated colonoscopy is assessed
- Perforation rate – the rate at which a perforation occurs during a diagnostic colonoscopy

The proportions used in these metrics vary between international endoscopic regulatory bodies, however the factors measured are uniform. Regular audit of these metrics allows identification of individual endoscopists who may require additional targeted training and allows minimization of risk to patients attending for colonoscopy.

Premalignant Lesions of the Colon Mucosa

There are several main types of lesions that can develop in the colon, each with its own characteristic endoscopic appearance and differing risks of malignant progression.

Adenomas

An adenoma is a focal lesion defined by the presence of a degree of dysplasia (at least low-grade dysplasia). Adenomas are a well-recognized precursor lesion of colorectal cancer though the adenoma–carcinoma pathway that is driven by mutations in the APC, KRAS, and TP53 genes and dysregulation of the transforming growth factor β (TGFβ) signaling pathway. As the adenoma acquires progressive mutations, this leads to increased proliferation and eventually invasive malignancy (Fearon and Vogelstein 1990; Smit et al. 2020). Adenomas can present in many different shapes, including flat, sessile and pedunculated. The risk of malignancy is increased with increasing size, an ulcerated depression in part of the lesion and a disorganized or absent vascular pattern seen on either white light or with enhanced endoscopic imaging techniques. The incidence of adenoma increases with age. It is estimated to be around 20–30% in large cohorts of asymptomatic patient undergoing colonoscopy (Ferlitsch et al. 2011; Kim et al. 2014).

Hyperplastic Polyps

Hyperplastic polyps are bland and usually diminutive lesions. In contrast to an adenoma a hyperplastic polyp never contains any degree of dysplasia. Histologically the luminal side of the hyperplastic crypts has a serrated (saw-tooth) appearance and the crypts are star-shaped on cross-section. Hyperplastic polyps are often found in the sigmoid colon and rectum and are thought to have no malignant potential. Hyperplastic polyps are quite common, with a prevalence around 20% (Hazewinkel et al. 2014; Kim et al. 2014).

Sessile Serrated Lesions

Similar to a hyperplastic polyp, a sessile serrated lesion also has serrated crypts, but in contrast to the hyperplastic polyp a sessile serrated lesion also has architectural disturbances at the crypt base. On histological examination the crypt base is widened with a basal horizontal extension, giving the appearance of a L or inverted T-shaped crypt base.

Endoscopically, sessile serrated lesions can be found throughout the colon but especially in the right side of the colon and often present as flat or slightly elevated pale lesions that are easily missed. Sessile serrated lesions do carry a risk of malignant progression and it is estimated that at least 10% of all sporadic colon cancers derive from sessile serrated lesions (García-Solano et al. 2010; Mäkinen et al. 2001). The molecular sequence of malignant progression is distinct from the adenoma-carcinoma sequence and involves mutations in KRAS and BRAF and widespread CpG island methylation and microsatellite instability. The prevalence of sessile serrated lesions is around 5% (Hazewinkel et al. 2014; Kim et al. 2014).

Traditional Serrated Adenoma

Traditional serrated adenomas are characterized by the presence of serrated crypts, prominent eosinophilic cytoplasm and ectopic crypts. Traditional serrated adenomas are most often found in the sigmoid colon and rectum and endoscopically present as pedunculated or sessile lesions. They are often KRAS and BRAF mutated but, unlike sessile serrated lesions, often lack microsatellite instability. Traditional serrated adenomas are rare with a prevalence of less than 1% (Hazewinkel et al. 2014; Kim et al. 2014) Dysplasia has been described in traditional serrated adenomas (Kim et al. 2010) but the risk of malignant progression is currently unclear, possibly reflecting their low incidence.

Classification Systems

Multiple classification systems for premalignant colonic lesions have been developed. They allow for a standardized description of lesions encountered and also provide information on the malignant potential and the risk of deep invasion.

Paris Classification

The Paris system is used to classify superficial lesions of the gastrointestinal tract based on their shape (Participants in the Paris Workshop 2003). Lesions are best observed using white light. Somewhat confusing, all lesions in the Paris classification are type 0 lesions; this is because the Paris classification was an extension of a previous classification for advanced gastric cancers (the Borrmann classification, that grades lesions from type 1 to type 4). The type 0 classification was added to describe superficial lesions and has the following subdivisions:

- Type 0-I (polypoid lesions) which includes the subtype 0-Ip for pedunculated and 0-Is for sessile lesions.
- Type 0-II (non-polypoid) which included the subtype 0-IIa for slightly elevated, 0-IIb for flat and-IIc for slightly depressed lesions.
- Type 0-III that described excavated lesions with an ulcerative appearance and suggests submucosal invasion.

Some lesions are best described by a combination of Paris classifications; for example, a slightly elevated lesion with a central depression can be describes as type 0-IIa+IIc.

The Paris classification can be used to estimate submucosal invasion, the change of which is increased in type 0-IIc and in particular in type 0-III lesions.

NICE Classification

The NBI International Colorectal Endoscopic (NICE) classification system uses NBI to classify lesions (Hewett et al. 2012). It looks at the color of the lesion, vessels and surface pattern to classify lesions in one of three categories:

- Type 1: color same or lighter than background, none or isolated lacy vessels, and a surface pattern of uniform white or dark spots suggests a hyperplastic lesion
- Type 2: color darker than background, brown vessels surrounding white structures and a surface pattern of oval, tubular or branched white structures suggests an adenoma
- Type 3: color darker than background with sometimes patchy white areas, disorganized or missing vessels, and an amorphous or absent surface pattern suggests a submucosal invasion.

While the Paris and NICE classification are the most commonly used in the western world, there are a number of other classification system that use NBI imaging that look at microvessel pattern (SANO, Jikei), surface pattern (Showa) or a combination of both (Hiroshima, JNET). These classification systems were all developed in Japan and are commonly used in Asia.

WASP Classification

Most classification systems do not allow differentiation between hyperplastic polyps and sessile serrated lesions. The increasing recognition that these two lesions are biologically distinct entities led to the development of the Workgroup serrAted polypS and Polyposis (WASP) classification (Jeg et al. 2016). It identifies four characteristics to identify sessile serrated polyps under narrow band imaging: a clouded surface, indistinct border, irregular shape and dark spots inside crypts. The presence of at least two criteria is sufficient to label a lesion a sessile serrated polyp.

Resection of Colorectal Lesions

Endoscopic resection of colorectal lesions provides a spectrum of complexity from simple snare resection of small lesions through to complex resection techniques allowing very large premalignant lesions to be removed. Advanced resection techniques are a subspecialty within the field of endoscopy and referral to an appropriately trained endoscopist is essential in providing the best outcome in terms of complete resection and reduced risk of complications. It is currently practice to remove the vast majority of any detected polypoid lesion of the colon at colonoscopy, and as the most commonly found are small lesions all colonoscopists are trained to undertake resection of these.

Snare Polypectomy

The majority of colorectal polyps can be resected at the index colonoscopy using snare polypectomy. A wire loop is placed over the lesion and closed around it. The lesion is then either removed using a cold snare technique in which the wire of the snare is designed to cut through mucosal tissue or using an electrosurgical diathermy machine to provide coagulation of any vasculature supplying the lesion – known as a "hot snare". Typically, a small sessile lesion less than 6 mm in size (Paris Classification 0-Is or 0-IIa, b or c) will be removed with a cold snare technique while pedunculated lesions using a hot snare.

Endoscopic Mucosal Resection (EMR)

EMR was first described in 1973 using a hypertonic saline solution to provide separation of the mucosal and muscularis tissue planes to allow dissection of a lesion (Deyhle et al. 1973). The technique is now a standard practice for colonoscopists to ensure safe resection of sessile lesions greater than 1 cm in size.

The technique involves a needle injector device through the working channel of the colonoscope to lift the lesion away from the muscularis. The injected solution can vary, but is usually a combination of adrenaline, colloid and a blue stain such as methylene blue or indigocarmine dye. This solution temporarily colors the underlying muscularis blue to allow the endoscopist to visualize that the resection margin is adequate and that the wall of the colon is intact. Lifting the lesion to be resected away from the underlying muscle using the injected solution reduces the risk of perforation.

Once a lesion is adequately lifted, a snare device is placed around the lesion and combined electrosurgical current of coagulation and cutting is used to remove it. Larger lesions are removed piecemeal, with sections removed piece by piece until the resection is completed. For the resection of flat colorectal lesions, the utilization of cold snare EMR appears to be as effective as using electrosurgical snaring at complete resection, while reducing the risk of perforation and having similar risk of bleeding. Figure 1 demonstrates a large laterally spreading tumor of the ascending colon, lifted and removed with EMR.

Following EMR a number of techniques have been examined in the literature including coagulation of the margin with either argon plasma coagulation or using diathermy application via the tip of a snare (Katsinelos et al. 2019; Kemper et al. 2021; Motchum et al. 2022). It is not definitively clear whether these techniques provide any advantage over endoscopically assessing complete resection combined with snare resection of remaining margins of adenoma.

The risks of EMR are bleeding, perforation and incomplete resection. The risk of bleeding is around 3% and depends on lesion size, patient comorbidity and use of anticoagulation (De Ceglie et al. 2016; Ferlitsch et al. 2017). Perforation risk is around 1% (De Ceglie et al. 2016; Heldwein et al. 2005). The risk of incomplete resection increases with lesion size and use of piecemeal resection.

Endoscopic Submucosal Dissection (ESD)

ESD allows the "en-bloc" resection of lesions. The technique requires advanced training and is carried out in a limited number of centers internationally. The lesion is lifted in a similar manner to an EMR, however rather than utilizing snare resection, a specially designed electrosurgical knife is used to dissect between the lesion and submucosal plane. The lesion is then removed as a single surgical sample. The technique has a slightly higher bleeding risk (1–2%) and increased perforation risk (5–8%) compared with EMR (De Ceglie et al. 2016; Hong et al. 2016; Lee et al. 2013; Okamoto et al. 2017) but for large lesions the risk of recurrence is lower. The procedure also takes significantly longer to perform than an EMR.

EMR and ESD techniques complement each other, however limitations in the number of centers providing ESD is currently prohibitive in offering it to all patients.

Full Thickness Resection (FTR)

The endoscopic FTR technique is relatively new technology, emerging in 2014. This allows a lesion to be resected by removing the entire thickness of the colon or rectum. The lesion is marked around the margin using a diathermy marker and is then pulled into a cap which has a clip and a snare fitted to it. The clip is then deployed and the snare cuts through the tissue pulled into the cap. This technique has evidence emerging that it can be utilised in the removal of early T1 colorectal cancers and for the completion of polypectomy in which scarring following EMR or ESD means that these techniques are unable to provide endoscopic resection of remnant adenomatous tissue.

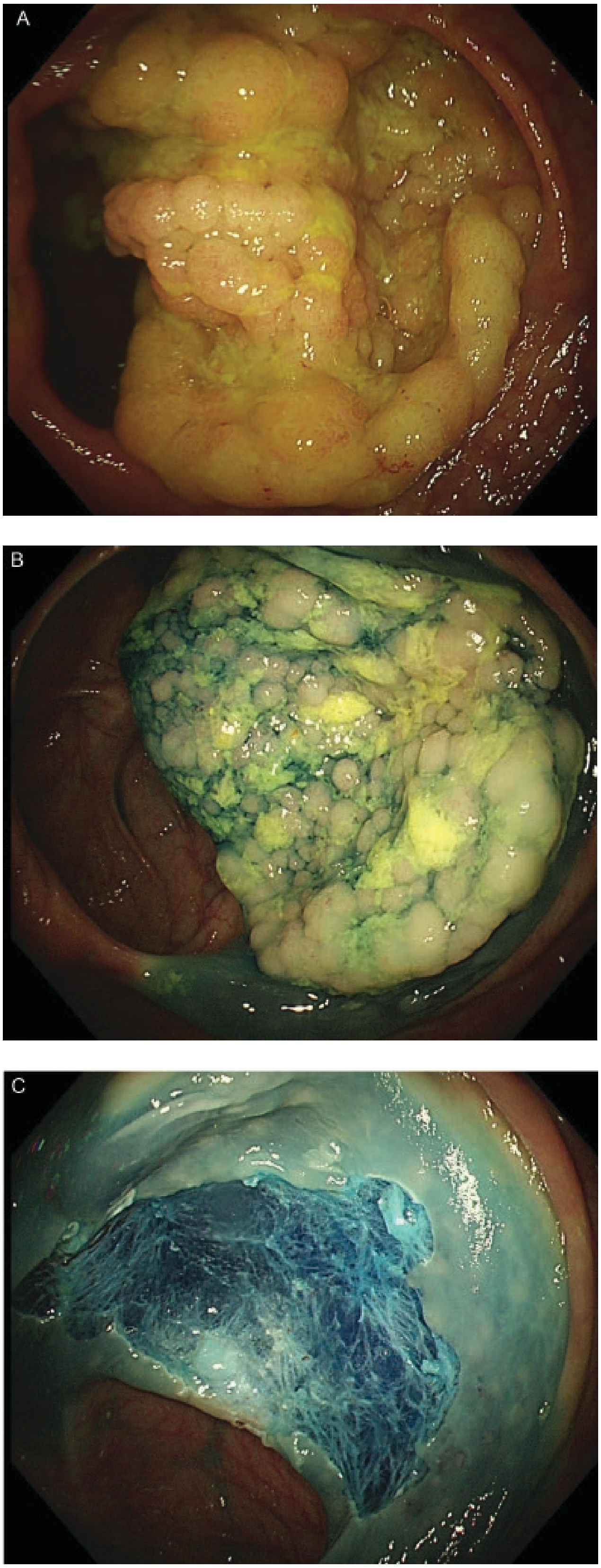

Figure 1 (A) Laterally spreading tumor of the ascending colon. (B) Lifting solution applied. (C) Resection site of the lesion with muscle stained blue.

Endoscopic Stenting of Colorectal Lesions

The rate of large bowel obstruction due to colon cancer is estimated to be around 8% – 13% of all patients with colorectal cancer (Cheynel et al. 2007; Jullumstrø et al. 2011; Winner et al. 2013). Historically, emergency surgical interventions (resection or the creation of a decompression stoma) have been the standard approach for patients with a malignant obstruction of the colon. However, in the last decades endoscopic stenting has emerged as an alternative to emergency surgery.

A colonic stent is a self-expanding nickel-titanium alloy cylinder that may be covered with a plastic outer layer or be bare metal (often termed covered and uncovered metal stents). The malignant stricture is approached with the colonoscope and guidewire is passed through it followed by a catheter, using radiological screening. An injection of contrast proximal to the stricture confirms the guidewire is correctly located and the stent is then placed across the guidewire and deployed. The main risk of colorectal stent placement is perforation of the malignant lesion, however there is no difference in mortality for patients presenting with obstruction managed surgically or with endoscopic stenting (Veld et al. 2020). Figure 2 demonstrates a colorectal stent after endoscopic placement.

Endoscopic Surveillance of Benign and Malignant Colorectal Pathology

The surveillance of colorectal lesions will vary internationally, however the principles are the same throughout. Patients presenting with benign colorectal lesions such as adenomas and sessile serrated lesions can be risk stratified based on the number and size of the lesions detected at the index colonoscopy. Following this stratification, a surveillance pathway is followed to ensure risk reduction for developing colorectal cancer in the future.

In the United Kingdom, the stratification is based on the index colonoscopy being of high quality, and a repeat colonoscopy is recommended in the case of either poor bowel preparation or incomplete colonoscopy. Provided the index colonoscopy is completed to a satisfactory standard the stratification is made into high risk or low risk. Low risk patients are not offered any surveillance colonoscopy, however the guidance does allow for clinical judgement to be applied to younger patients falling into a low risk category. High risk patients are those with either 5 or more adenomas or 2 or more adenomas where 1 is greater than 10 mm in size. The high risk group are offered a colonoscopy in 3 years and the risk stratification is applied again at this appointment (Rutter et al. 2020).

If at the index colonoscopy a large lesion requiring advanced resection such as EMR or ESD is detected, then after resection a site check is performed between 2 and 6 months following resection. After this, a one-year surveillance colonoscopy and then a three-year surveillance colonoscopy are performed. At the three-year surveillance colonoscopy the risk stratification is applied again. For patients with colorectal cancer a surveillance is offered at 1 year and then 3 years, unless there was an impassable cancer in which case colonoscopy is offered as soon as is considered safe (usually around 3 months) following surgical resection.

Conclusion

Endoscopic techniques for the detection, assessment and resection of colorectal neoplastic pathology have developed over the past 30 years to allow non-surgical management of such lesions. This has allowed reductions in the risk to patients in treating

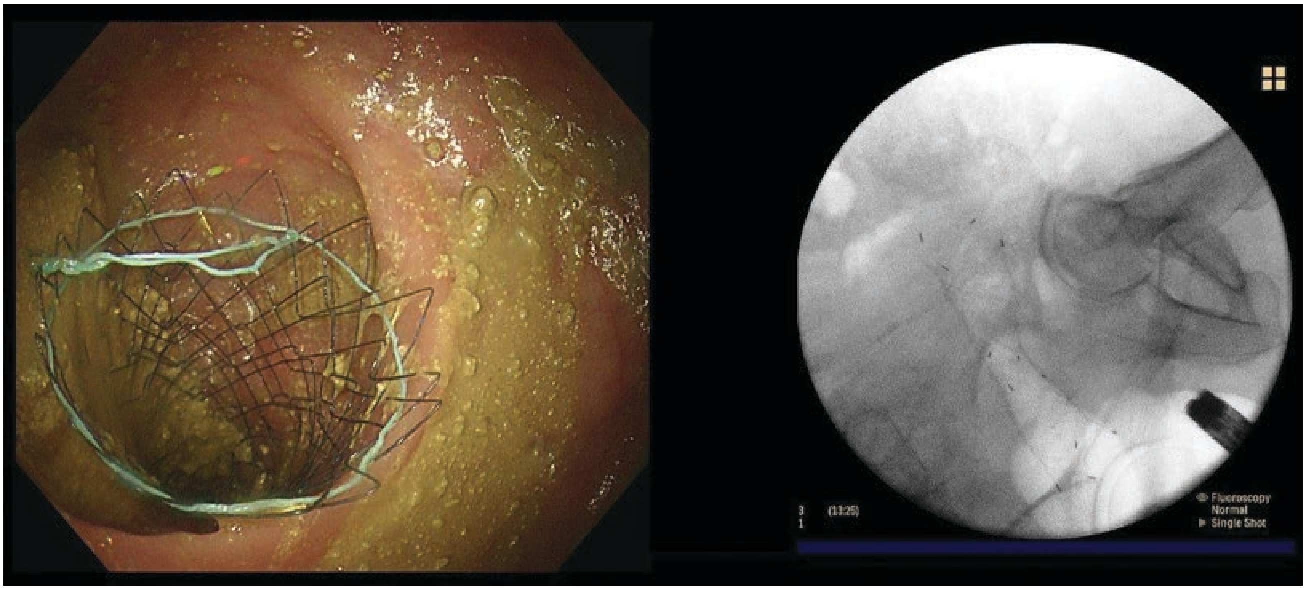

Figure 2 Endoscopically inserted self-expanding stent.

these lesions by moving them from surgical treatment pathways into endoscopic treatment.

Key Points of Current Management

1 Colonoscopy is the gold standard in the diagnosis of colorectal neoplastic pathology.
2 Quality in colonoscopy is the single most important factor in ensuring that colorectal cancers are detected at the index procedure.
3 Endoscopic imaging technology has improved with enhanced resolution, image manipulation and artificial intelligence to help the endoscopist in making a diagnosis.
4 Endoscopic resection techniques now provide safe and effective management of large colorectal benign lesions and often allow patients to avoid surgical resections.
5 Endoscopic stenting of colorectal lesions is a potential treatment option in patients presenting with large bowel obstruction due to colorectal cancer.

Areas for Further Research

1 How will artificial intelligence in colonoscopy assist endoscopists in the reduction of post colonoscopy colorectal cancer?
2 What techniques at the time of EMR will reduce the risk of adenoma recurrence?
3 For circumferential colorectal lesions not suitable for surgical intervention, what is the best timing for placement of a colorectal stent?

Trusted Links for Further Reading

Key performance indicators for colonoscopy: Rees CJ, Thomas Gibson S, Rutter MD, Baragwanath P, Pullan R, Feeney M, e.a. UK key performance indicators and quality assurance standards for colonoscopy. Gut. Dec 2016;65(12):1923–9. https://www.bsg.org.uk/clinical-resource/uk-key-performance-indicators-and-quality-assurance-standards-for-colonoscopy

How to Manage Large Colorectal Polyps EMR vs. ESD. UEGWeek2012_Syllabus_121002.indd

Crockett SD, Nagtegaal ID. Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. Gastroenterology. Oct 2019;157(4):949–966.e4. https://www.gastrojournal.org/article/S0016-5085(19)41115–3/fulltext

References

Atkinson, N.S.S., Ket, S., Bassett, P. et al. (2019 Aug). Narrow-band imaging for detection of neoplasia at colonoscopy: a meta-analysis of data from individual patients in randomized controlled trials. *Gastroenterology* 157 (2): 462–471.

Brown, S.R., Baraza, W., Din, S., and Riley, S. (2016 Apr). Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *Cochrane Database Syst Rev* 7 (4): CD006439.

Cheynel, N., Cortet, M., Lepage, C. et al. (2007 Oct). Trends in frequency and management of obstructing colorectal cancers in a well-defined population. *Dis Colon Rectum* 50 (10): 1568–1575.

De Ceglie, A., Hassan, C., Mangiavillano, B. et al. (2016 Aug). Endoscopic mucosal resection and endoscopic submucosal dissection for colorectal lesions: a systematic review. *Crit Rev Oncol Hematol* 104: 138–155.

Deyhle, P., Largiadèr, F., Jenny, S., and Fumagalli, I. (1973 Feb). A method for endoscopic electroresection of sessile colonic polyps. *Endoscopy* 5 (1): 38–40.

Fearon, E.R. and Vogelstein, B. (1990 Jun 1). A genetic model for colorectal tumorigenesis. *Cell* 61 (5): 759–767.

Ferlitsch, M., Moss, A., Hassan, C. et al. (2017 Mar). Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 49 (3): 270–297.

Ferlitsch, M., Reinhart, K., Pramhas, S. et al. (2011 Sep 28). Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. *JAMA* 306 (12): 1352–1358.

Froehlich, F., Wietlisbach, V., Gonvers, J.J. et al. (2005 Mar). Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 61 (3): 378–384.

García-Solano, J., Pérez-Guillermo, M., Conesa-Zamora, P. et al. (2010 Oct). Clinicopathologic study of 85 colorectal serrated adenocarcinomas: further insights into the full recognition of a new subset of colorectal carcinoma. *Hum Pathol* 41 (10): 1359–1368.

Gong, D., Wu, L., Zhang, J. et al. (2020 Apr). Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomized controlled study. *Lancet Gastroenterol Hepatol* 5 (4): 352–361.

Hazewinkel, Y., de Wijkerslooth, T.R., Stoop, E.M. et al. (2014 Mar). Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy. *Endoscopy* 46 (3): 219–224.

Heldwein, W., Dollhopf, M., Rösch, T. et al. (2005 Nov). The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. *Endoscopy* 37 (11): 1116–1122.

Hewett, D.G., Kaltenbach, T., Sano, Y. et al. (2012 Sep). Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology* 143 (3): 599–607.e1.

Hong, S.N., Byeon, J.S., Lee, B.I. et al. (2016 Jul). Prediction model and risk score for perforation in patients undergoing colorectal endoscopic submucosal dissection. *Gastrointest Endosc* 84 (1): 98–108.

Jeg, I., Bastiaansen, B.A.J., van Leerdam, M.E. et al. (2016 Jun). Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. *Gut* 65 (6): 963–970.

Jullumstrø, E., Wibe, A., Lydersen, S., and Edna, T.H. (2011 May). Colon cancer incidence, presentation, treatment and outcomes over 25 years. *Colorectal Dis* 13 (5): 512–518.

Katsinelos, P., Lazaraki, G., Chatzimavroudis, G. et al. (2019). A retrospective comparative study of argon plasma versus polypectome snare tip coagulation: effect on recurrence rate after resection of large laterally spreading type lesions. *Ann Gastroenterol* 32 (2): 178–184.

Kemper, G., Turan, A.S., Schoon, E.J. et al. (2021 Oct). Endoscopic techniques to reduce recurrence rates after colorectal EMR: systematic review and meta-analysis. *Surg Endosc* 35 (10): 5422–5429.

Kim, H.Y., Kim, S.M., Seo, J.H. et al. (2014 Apr 28). Age-specific prevalence of serrated lesions and their subtypes by screening colonoscopy: a retrospective study. *BMC Gastroenterol* 14: 82.

Kim, K.M., Lee, E.J., Kim, Y.H. et al. (2010 May). KRAS mutations in traditional serrated adenomas from Korea herald an aggressive phenotype. *Am J Surg Pathol* 34 (5): 667–675.

Lee, C.K., Lee, S.H., and Hwangbo, Y. (2011 Sep). Narrow-band imaging versus I-Scan for the real-time histological prediction of diminutive colonic polyps: a prospective comparative study by using the simple unified endoscopic classification. *Gastrointest Endosc* 74 (3): 603–609.

Lee, E.J., Lee, J.B., Lee, S.H. et al. (2013 Jan). Endoscopic submucosal dissection for colorectal tumors–1,000 colorectal ESD cases: one specialized institute's experiences. *Surg Endosc* 27 (1): 31–39.

Mäkinen, M.J., George, S.M., Jernvall, P. et al. (2001 Mar). Colorectal carcinoma associated with serrated adenoma–prevalence, histological features, and prognosis. *J Pathol* 193 (3): 286–294.

McGill, S.K., Evangelou, E., Ioannidis, J.P.A. et al. (2013 Dec). Narrow band imaging to differentiate neoplastic and non-neoplastic colorectal polyps in real time: a meta-analysis of diagnostic operating characteristics. *Gut* 62 (12): 1704–1713.

Motchum, L., Levenick, J.M., Djinbachian, R. et al. (2022 Jun 17). Endoscopic mucosal resection combined with hybrid argon plasma coagulation to prevent recurrence of large nonpedunculated colorectal polyps. *Gastrointest Endosc* 96 (5): 840–848.e2. S0016-5107(22)01769-2.

Okamoto, K., Watanabe, T., Komeda, Y. et al. (2017). Risk Factors for Postoperative Bleeding in Endoscopic Submucosal Dissection of Colorectal Tumors. *Oncology* 93 (Suppl 1): 35–42.

Participants in the Paris Workshop. (2003 Dec). The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 58 (6 Suppl): S3–43.

Rees, C.J., Rajasekhar, P.T., Wilson, A. et al. (2017 May). Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. *Gut* 66 (5): 887–895.

Rees, C.J., Thomas Gibson, S., Rutter, M.D. et al. (2016 Dec). UK key performance indicators and quality assurance standards for colonoscopy. *Gut* 65 (12): 1923–1929.

Repici, A., Badalamenti, M., Maselli, R. et al. (2020 Aug). Efficacy of real-time computer-aided detection of colorectal neoplasia in a randomized trial. *Gastroenterology* 159 (2): 512–520.e7.

Rutter, M.D., East, J., Rees, C.J. et al. (2020 Feb 1). British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 69 (2): 201–223.

Smit, W.L., Spaan, C.N., Johannes de Boer, R. et al. (2020 Oct 13). Driver mutations of the adenoma-carcinoma sequence govern the intestinal epithelial global translational capacity. *Proc Natl Acad Sci U S A* 117 (41): 25560–25570.

Spadaccini, M., Iannone, A., Maselli, R. et al. (2021 Oct). Computer-aided detection versus advanced imaging for detection of colorectal neoplasia: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 6 (10): 793–802.

Subramanian, V., Mannath, J., Hawkey, C.J., and Ragunath, K. (2011 Jun). High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 43 (6): 499–505.

Veld, J.V., Amelung, F.J., Borstlap, W.A.A. et al. (2020 Mar 1). Comparison of decompressing stoma vs stent as a bridge to surgery for left-sided obstructive colon cancer. *JAMA Surg* 155 (3): 206–215.

Wang, P., Liu, X., Berzin, T.M. et al. (2020 Apr). Effect of a deep-learning computer-aided detection system on adenoma detection during colonoscopy (CADe-DB trial): a double-blind randomised study. *Lancet Gastroenterol Hepatol* 5 (4): 343–351.

Winner, M., Mooney, S.J., Hershman, D.L. et al. (2013 Aug). Incidence and predictors of bowel obstruction in elderly patients with stage IV colon cancer: a population-based cohort study. *JAMA Surg* 148 (8): 715–722.

Imaging and Staging of Colorectal Cancer

Jeremy Meyer, David Bowden & Justin Davies

Introduction

The treatment of colorectal cancer is almost invariably surgical, involving the removal of the primary lesion and, if possible and indicated, the removal of metastatic (secondary) lesions. The only exception to this paradigm is represented by patients for whom a "watch and wait" strategy has been adopted after complete clinical response following neoadjuvant treatment for rectal cancer. The prognosis of colorectal cancer has improved over the last decades, notably following the introduction of total mesorectal excision (TME) for rectal cancer and of neoadjuvant treatment for preoperative downstaging rectal cancer. The indication for neoadjuvant treatment is historically based on the stage of the tumor and its relation to adjacent anatomical structures, adequate pre-operative staging by modern imaging techniques being key for optimal surgical and oncological planning. However, more recent guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom recommend neoadjuvant treatment for all patients with rectal cancer (NIfHaCE 2020), although this has been met with some challenge (Davies et al. 2022). Further, identifying patients with locally advanced cancer who will require multidisciplinary surgical input, or those with metastatic disease, is mostly the remit of expert gastrointestinal radiologists working within multidisciplinary teams.

The objectives of imaging for colorectal cancer are therefore multiple. The first objective of imaging is to identify and stage the primary lesion, in terms of local extension but also in terms of potentially metastatic lymph nodes, in order to assess surgical resectability and to decide on the surgical procedure required and the possible need for multivisceral or *en bloc* resection to achieve clear resection margins. In patients with rectal cancer, resectability can be reassessed after neo-adjuvant treatment. The second objective is to check for the presence of potentially distant metastases, either in central lymph nodes not accessible to conventional surgery, in other organs or in the peritoneal cavity. Finally, the third objective is to rule out the presence of a synchronous lesion in the gastrointestinal tract, especially in patients with a genetic predisposition to colorectal cancer.

Colon Cancer

Recommended Imaging

The minimum required imaging for colon cancer consists of a CT of the abdomen and pelvis to characterize the primary cancer and its relation to anatomical structures (cT stage), the eventual presence of enlarged lymph nodes (cN stage) and the eventual presence of distant metastases (cM stage), associated with a CT of the chest to look for lung metastases. The liver, an organ at risk for colorectal cancer metastases due to its filtering function of the portal blood flow, is assessed by the abdominal CT with, in case of doubt, a dedicated Primovist contrast liver MRI. The presence of a synchronous cancer in the colon is assessed using a complete colonoscopy in an adequately prepared patient or, if colonoscopy cannot be performed, a CT colonography. In case the recommended imaging cannot be performed before the removal of the primary lesion, which can be the case – for example – in a patient with an obstructing sigmoid cancer, the examinations to rule out metastatic disease and synchronous cancer should be performed when the clinical situation allows, but ideally within three months (Argiles et al. 2020).

Classification System

The classification of the primary cancer and its eventual secondary lesions relies on the latest version of the Union for International Cancer Control (UICC) TNM system (Table 1). However, as this classification is – in the context of preoperative imaging – provisional, it is usually preceded by a “c” (meaning “clinical”). For instance, if lymph nodes are enlarged on the preoperative CT, the provisional stage will indicate cN+ (or cN1 or cN2), but only the definitive histopathological analysis of the operative specimen will indicate if these lymph nodes contain metastatic cells (pN+) or not (pN0).

Assessing the Primary Lesion (T)

The gold standard for assessing the primary colon cancer lesion and its local extension is a CT of the abdomen and pelvis. The classical features of colorectal cancer on CT are usually either as a soft tissue mass or bowel wall thickening that may be associated with luminal narrowing (“apple core” appearance). The mass will typically enhance in a similar fashion to the bowel wall, though large lesions may undergo central necrosis. Texture analysis may help differentiating benign thickening of the bowel wall from colorectal cancer (Wang et al. 2020). Up to 41% of patients suffering from colorectal cancer are first diagnosed in the emergency setting (Bass et al. 2009). Therefore, large bowel obstruction or lower gastrointestinal bleeding should raise the suspicion of cancer, which should be investigated by colonoscopy.

If the colorectal cancer can be visualized by CT, this helps in defining its location, which is often less accurate when assessed by colonoscopy. The gold standard for localizing the tumor remains, however, surgical exploration and visualizing the distal tattoos placed by the endoscopist.

CT has moderate reliability for defining the T stage, which is correctly predicted in only 60% of patients (Smith et al. 2007) (Figure 1). The diagnostic accuracy of CT is lowest for early colorectal cancer, for which endoscopic ultrasound is better, although the clinical significance of accurately staging early

Table 1 TNM classification of colon and rectal cancer, adapted from the AJCC Cancer Staging Manual (8th Edition).

T stage	T1		Invasion of the submucosa by the primary tumor
	T2		Invasion of the muscularis propria by the primary tumor
	T3		Invasion of the subserosa by the primary tumor
	T4		Invasion of other organs/structures and/or the visceral peritoneum by the primary tumor
		T4a	Invasion of the visceral peritoneum by the primary tumor
		T4b	Invasion of nearby organs by the primary tumor
N stage	N0		No metastasis in regional lymph nodes
	N1		1–3 metastatic regional lymph node(s)
		N1a	1 metastatic regional lymph node
		N1b	2–3 metastatic regional lymph nodes
		N1c	No metastasis in regional lymph nodes but satellite cancer cells in the non-peritonealized tissues near the tumor
	N2		>3 metastatic regional lymph nodes
		N2a	4–6 metastatic regional lymph nodes
		N2b	>6 metastatic regional lymph nodes
M stage	M0		No distant metastasis
	M1		Distant metastasis(es)
		M1a	1 distant metastasis
		M1b	>1 distant metastasis
		M1c	Metastasis to the peritoneum (peritoneal carcinomatosis) with or without other organ(s)

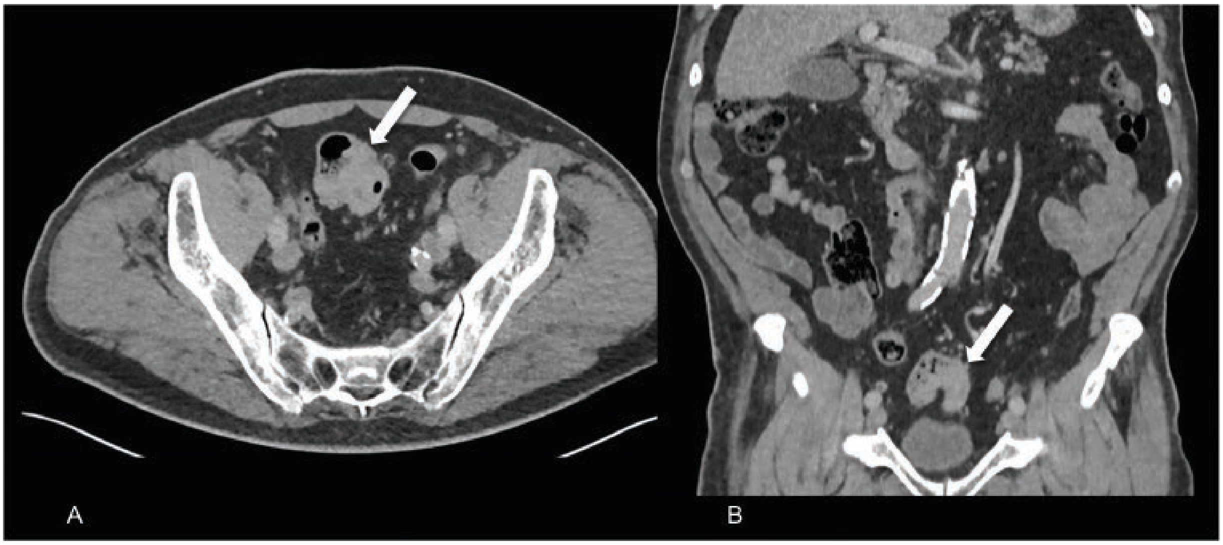

Figure 1 Axial (A) and coronal multiplanar reformat (MPR, (B)) image of a T2/3 sigmoid tumor (arrow). Resolution of CT is inadequate to reliably differentiate early stages of colorectal tumors given its inability to resolve bowel wall layers and differentiate T2 from T3 disease. Identification of T4a from T3 disease may also be challenging in the presence of benign desmoplastic change (not shown).

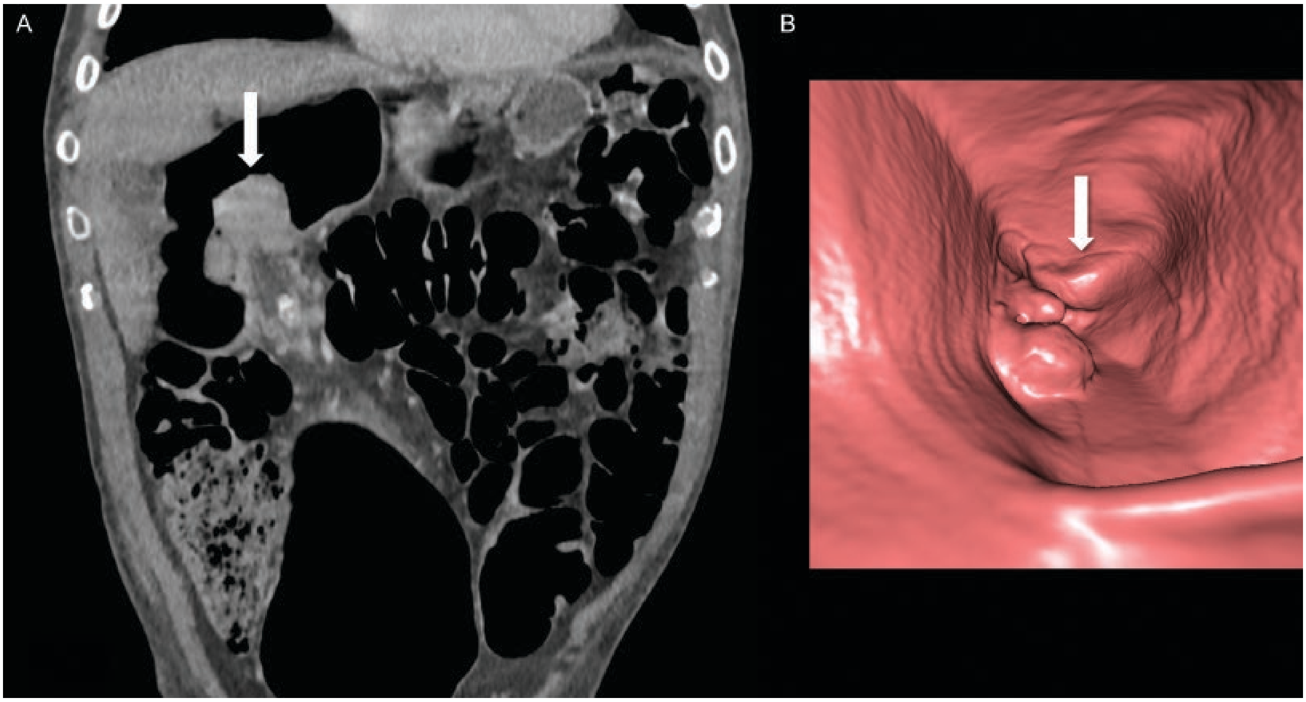

Figure 2 (A) Coronal multiplanar reformatted images of an apple core lesion of the hepatic flexure in a patient with colonic pseudo-obstruction. (B) Endoluminal virtual colonoscopic image of the tumor, generated from the same image data made possible by surrounding gaseous distension of the bowel.

colonic cancer by CT is of limited importance. CT is better for more advanced T stages. For instance, the sensitivity and specificity of CT to detect tumor invasion beyond the muscular propria are 86% and 78% respectively (Dighe et al. 2010). Of note, the presence of colon wall deformity, notably an apple core appearance, is highly predictive of stage T3 disease or higher (Flor et al. 2013) (Figure 2).

Distinguishing T3 from T4 disease is sometimes not possible, as identifying early progression into the peritoneum cannot be reliably made by CT. The involvement of other

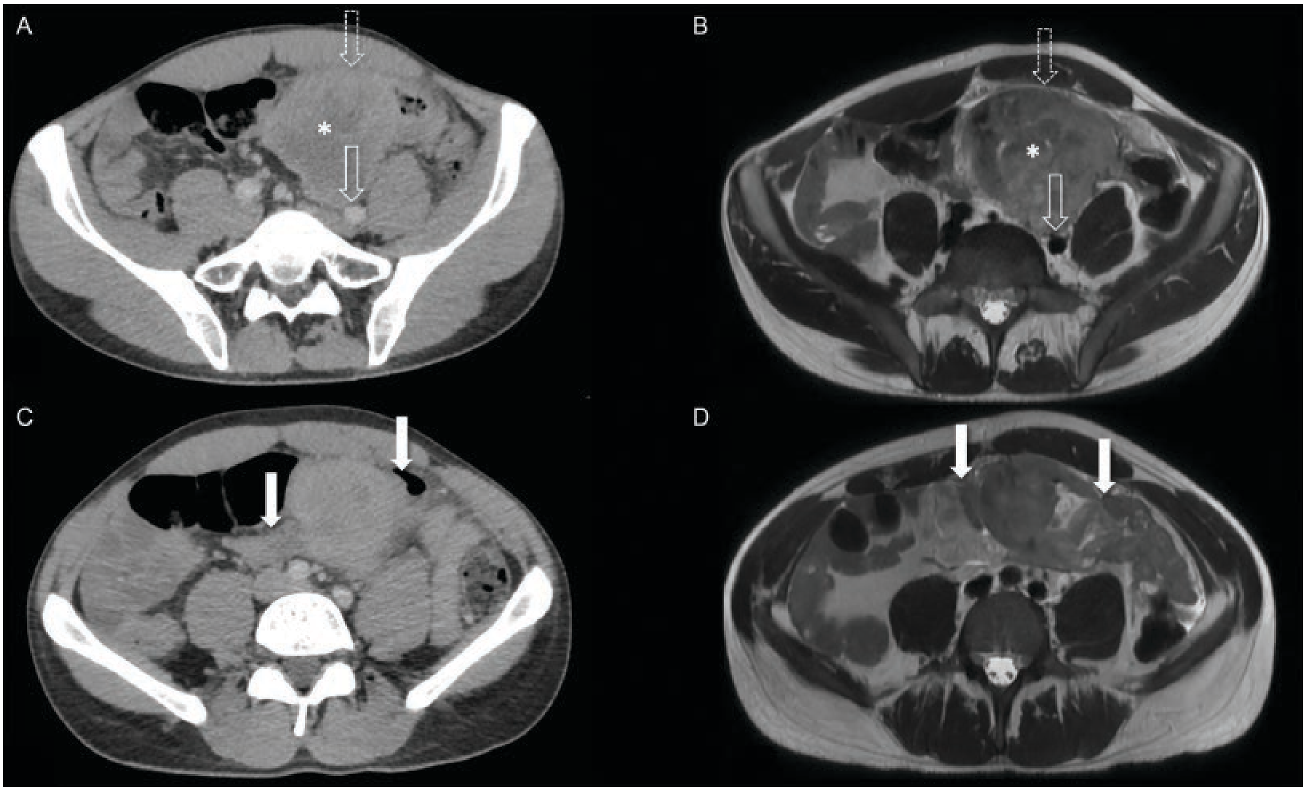

Figure 3 (A, C) Axial CT and (B, D) Axial T2-weighted MR image at corresponding levels of a large T4b sigmoid tumor (asterisk) involving the left common iliac artery (open arrow), transversalis fascia (dashed arrow) and adjacent small bowel loops (solid white arrows). Given the superior resolution of MRI its use is invaluable where there may be uncertainty regarding early adjacent organ invasion.

organs by direct tumor invasion is usually suggested by loss of the fat plane accompanied by spicular projections or more obvious invasion. Identification of T4 disease is of importance, as it may change the therapeutic management, both in terms of potential neo-adjuvant treatment (Body et al. 2021) and in terms of surgical strategy (Figure 3). It should be mentioned that CT has moderate sensitivity for assessing involvement of the retroperitoneal surgical margin (Elibol et al. 2016).

Preoperative CT with arterial and portal venous phase imaging also aids in the surgical planning where precise knowledge of the vascular anatomy and its variations (Alsabilah et al. 2017; Kuzu et al. 2017) is of importance, such as, for example, in patients who may be considered for complete mesocolic excision during which significant vascular complications are a risk.

Assessing Lymph Nodes (N)

The lymph node distribution of the colon is classified into the pericolic lymph nodes (D1), the intermediate lymph nodes (D2) and the central lymph nodes (D3). The Japanese classification for colorectal cancer numbers lymph node stations according to their anatomical locations (Japanese Society for Cancer of the C, Rectum 2019). The lymph node drainage of colorectal cancer follows the vascular axis feeding the tumor, and therefore potential metastatic lymph nodes should be expected along these axes. In right colon cancer, metastatic lymph nodes are found in 41.5% of patients. D2 lymph nodes contain metastatic deposits in 9.7% of patients, and D3 lymph nodes in 1.5% (Yamaoka et al. 2017). The presence of one or more metastatic lymph node(s) in colon cancer defines stage III disease. Retroperitoneal, pelvic or inguinal lymph node enlargement represent metastatic disease in patients with colon cancer.

CT has moderate accuracy for defining the N stage, which is correctly predicted in only 62% of patients (Smith et al. 2007). The sensitivity and specificity of CT for identifying metastatic lymph nodes in colorectal cancer are 70% and 78% respectively (Dighe et al. 2010). Of note, pathologically enlarged nodes may not contain metastatic cells and smaller nodes may have microscopic tumor involvement. Stage III disease is best predicted by the presence of one or more lymph node(s) with a heterogeneous density and/or an irregular outer border (Figure 4).

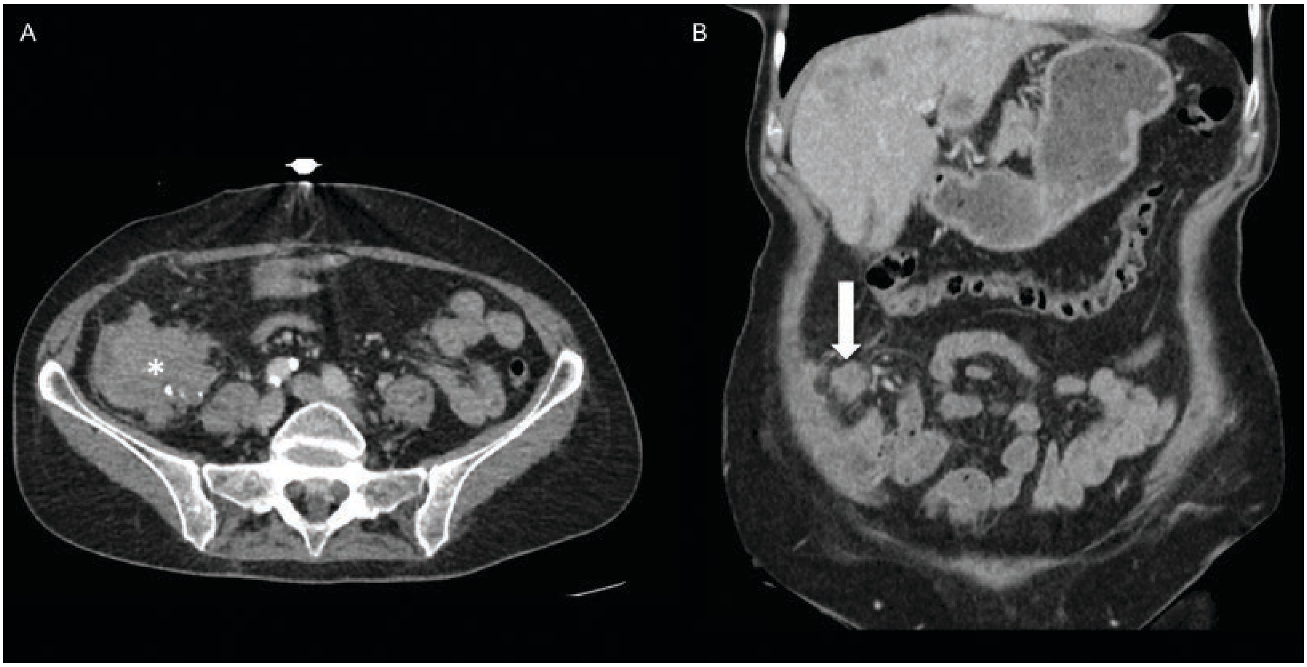

Figure 4 Axial CT image (A) and coronal MPR (b) of a large T4a caecal tumor (asterisk) with an adjacent irregular, heterogeneous attenuation and enlarged mesocolic lymph node (arrow). The combination of these imaging features is consistent with metastatic lymph node involvement.

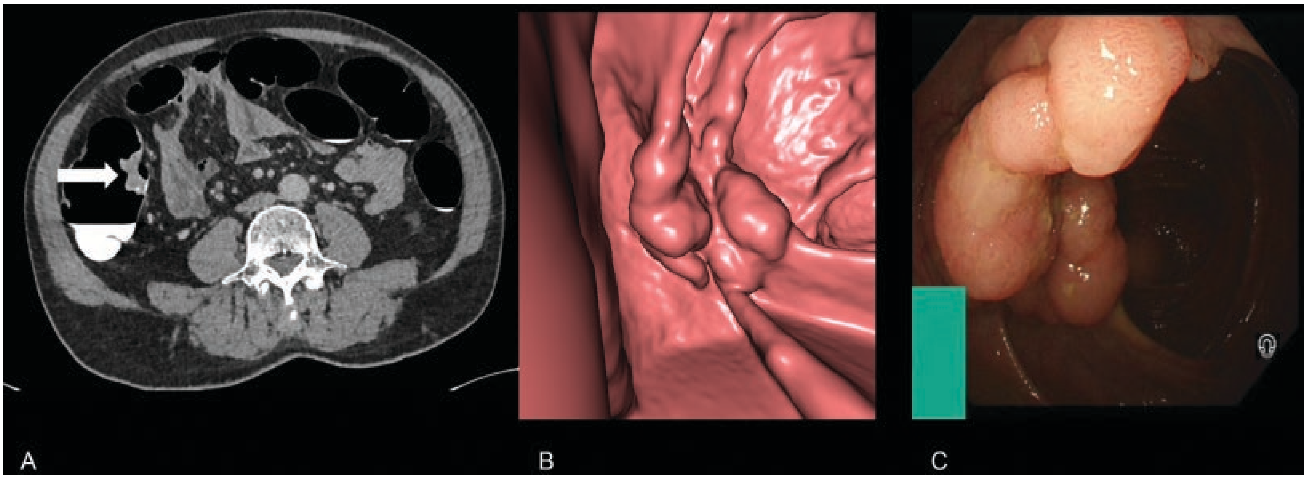

Figure 5 Axial CT Colonoscopy study image (A) of a 3 cm polypoid mass within the ascending colon (arrow). Insufflation of the colon with carbon dioxide distends the bowel wall, enabling identification of small polyps and the generation of virtual endoscopic, volume rendered images (B). The corresponding optical endoscopic image (C) correlates well with that generated by CT. High density material within the bowel lumen in (A) represents iodine-based oral contrast medium administered as part of bowel preparation – both to achieve a laxative effect and for "tagging" of any residual fecal material, improving the detection of small polyps.

Excluding Synchronous Lesions

Synchronous colorectal cancer refers to more than one primary colorectal cancer diagnosed in the same patient at the time of initial presentation. The prevalence of synchronous colorectal cancer is close to 4% of patients (Latournerie et al. 2008; Mulder et al. 2011). This prevalence is of course higher in patients with hereditary colorectal cancer, such as hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP) and others, and in those with chronic inflammation secondary to inflammatory bowel disease. Excluding synchronous lesions in the lower gastrointestinal tract during the preoperative assessment is key, as it may change the surgical strategy, often by performing a subtotal colectomy instead of a segmental colectomy. This is usually performed by a complete colonoscopy which also allows confirmation of the diagnosis (using biopsy), tattoo marking of the tumor site(s) and removal of pre-cancerous lesions. If a complete colonoscopy is not feasible, combining flexible sigmoidoscopy and CT colonography may constitute an alternative (Argiles et al. 2020). In the event a synchronous lesion cannot be excluded before the removal of the primary lesion, in situations such as emergency presentation, colonoscopy (preferentially) or CT-colonography can be performed when the clinical situation allows, but ideally within three months of emergency resection (Argiles et al. 2020).

CT colonography, also known as virtual colonoscopy, allows assessment of the colonic lumen using low-dose CT combined with oral contrast and CO^2 insufflation of the colon (Figure 5). CT colonography is usually indicated for colorectal cancer screening in patients refusing a more invasive procedure, for assessment of strictures and to assess the colon proximal to a partially obstructing colorectal cancer or for excluding synchronous lesion(s) in patients refusing complete colonoscopy or in whom a complete colonoscopy is unsuccessful. In patients with positive fecal occult blood testing, CT colonography has been reported to have a sensitivity and specificity of 88.8% and 75.4% respectively for the detection of colorectal cancer and adenomas ≥6 mm (Plumb et al. 2014a). Its sensitivity was demonstrated to be similar to the sensitivity of colonoscopy for the detection of polyps >5 mm (Graser et al. 2009), but was dependent on the expertise of the reporting radiologist (Plumb et al. 2014b).

Rectal Cancer

Recommended Imaging

The introduction of total mesorectal excision (TME) as a surgical technique and preoperative downstaging (chemo)radiotherapy have markedly improved both local recurrence rates and survival for patients with rectal cancer. The role of imaging is to provide detailed staging, including an assessment of the tumor in relation to the circumferential resection margin (CRM) and the presence or absence of poor prognostic factors, such as extramural venous invasion (EMVI). This will then allow discussion on the suitability and planning of optimal surgery and the need for neoadjuvant treatment.

The minimum required imaging for rectal cancer consists of CT imaging of the abdomen and pelvis to assess for enlarged lymph nodes (cN stage) and distant metastases (cM stage), in addition to CT imaging of the chest to evaluate for lung metastases. The primary lesion is optimally evaluated using pelvic MRI, which allows accurate locoregional staging by determining the cT stage and assessment of the circumferential resection margin (CRM). In the case of early rectal cancer, endoscopic ultrasound may be used as an adjunct to more precisely define the depth of invasion of T1 cancer, given the limitations of MRI in this specific area (Glynne-Jones et al. 2017).

Moreover, the tumor's distance to the anal verge and from the sphincters has to be assessed by a combination of digital rectal examination, rigid rectoscopy and pelvic MRI (Glynne-Jones et al. 2017), as it will help in surgical planning and whether a sphincter-preserving surgical approach may be an option.

The presence of a synchronous cancer in the colon is ruled out using a complete colonoscopy in an adequately prepared patient, or CT colonography. In the case of an obstructing rectal cancer, emergency resection of the primary rectal lesion is usually not performed and a surgical diversion by a loop stoma is the preferred option prior to further pre-operative staging and consideration of neo-adjuvant treatment.

Classification System

The classification of the primary cancer and its eventual secondary lesions relies on the latest version of the Union for International Cancer Control (UICC) TNM system, which is similar to the one used for colon cancer (Table 1). As this classification is – in the context of preoperative imaging – provisional, it is usually preceded by a "c" (meaning "clinical"). Alternatively, classification of the primary lesion can be preceded by the prefix "mr," meaning that the stage was provided by MRI, which is usual in rectal cancer. If neo-adjuvant treatment was given before imaging, existing prefix and/or stage indications are preceded by "y." This can be the case in the context of restaging after (chemo)radiotherapy.

Assessing the Primary Lesion (T)

MRI is the imaging modality of choice when performing the local staging of rectal cancer and usually helps to inform the therapeutic management. Therefore, quality of MRI reporting is key to optimal care, and the use of a structured template for MRI reporting is recommended (Glynne-Jones et al. 2017; Gupta et al. 2020), as depicted in Table 2. Alternatively, the Korean Society of Abdominal Radiology (KSAR) template can be used (Cancer KSGfR 2017).

Depth of Invasion

At MRI the mucosal layer of the bowel wall appears as a fine, low signal intensity line with the thicker, higher signal intensity submucosal layer beneath. The muscularis propria is seen as a low-intensity outer layer that may occasionally be depicted as two distinct layers – the inner circular layer and the outer longitudinal layer. The outer layer has an irregular corrugated appearance and numerous surface interruptions caused by vessels entering the rectal wall. The perirectal fat displays high signal intensity with vessels depicted as signal voids within, while the mesorectal fascia is visible as a fine, low signal layer enveloping the perirectal fat and rectum (Brown et al. 1999). Tumors typically appear as intermediate signal lesions on T2-weighted MRI, being of higher signal than muscle but lower than fat or the rectal submucosa.

Given its higher resolution, endorectal ultrasound allows better definition of the layers of the rectal wall than MRI. Images demonstrate a hyperechogenic line (interface with the probe), the mucosa and muscularis mucosae (hypoechogenic line), the submucosa (hyperechogenic line), the muscularis propria (hypoechogenic line) and the perirectal tissue (peritoneum or mesorectum, hyperechogenic line) (Nuernberg et al. 2019). Endorectal ultrasound is not routinely performed for staging of rectal cancer, but can be used for pre-operative assessment of early tumors and in patients in whom MRI is contra-indicated such as those with incompatible pacemakers or cerebral aneurysm clips. It has a pooled sensitivity and specificity to determine T1 stage of 87.8% and 98.3%, respectively (Puli et al. 2009) and allows early and locally advanced rectal cancer to be differentiated with 96% sensitivity and 85% specificity (Zorcolo et al. 2009) (Figure 6). Precise pre-operative substaging of T1 tumors into the sm1/sm2/sm3 Kikuchi stages

Table 2 Example of standardized case-report form for pelvic MRI to assess rectal cancer.

Patient identifiants:
Clinical indication:
Date:
Contrast product:
Tumor location (lower <5 cm, middle 5-10 cm, upper 10-15 cm from anal verge)
Distal tumor to anal verge (cm)
Distal tumor to top of puborectalis muscle (cm)
Length of tumor (cm)
Tumor at or below the top of puborectalis (yes/no)
Relationship to peritoneal reflection (above/below)
Clock face of tumor
Morphology of tumor
Mucinous (yes/no)
Extramural depth of invasion (mm)
Tumor/EMVI/node closest to MRF (mm, clock face)
Structure closest to MRF (tumor/EMVI/node)
Clock face of closest MRF
MRF involved? (yes, if ≤ 1 mm)
T stage
T4b involvement (detail)
EMVI (and location)
Mesorectal lymph nodes
Pelvic side wall nodes (number, side, location)
N stage
Other findings
Conclusion (mrTNM stage, MRF)

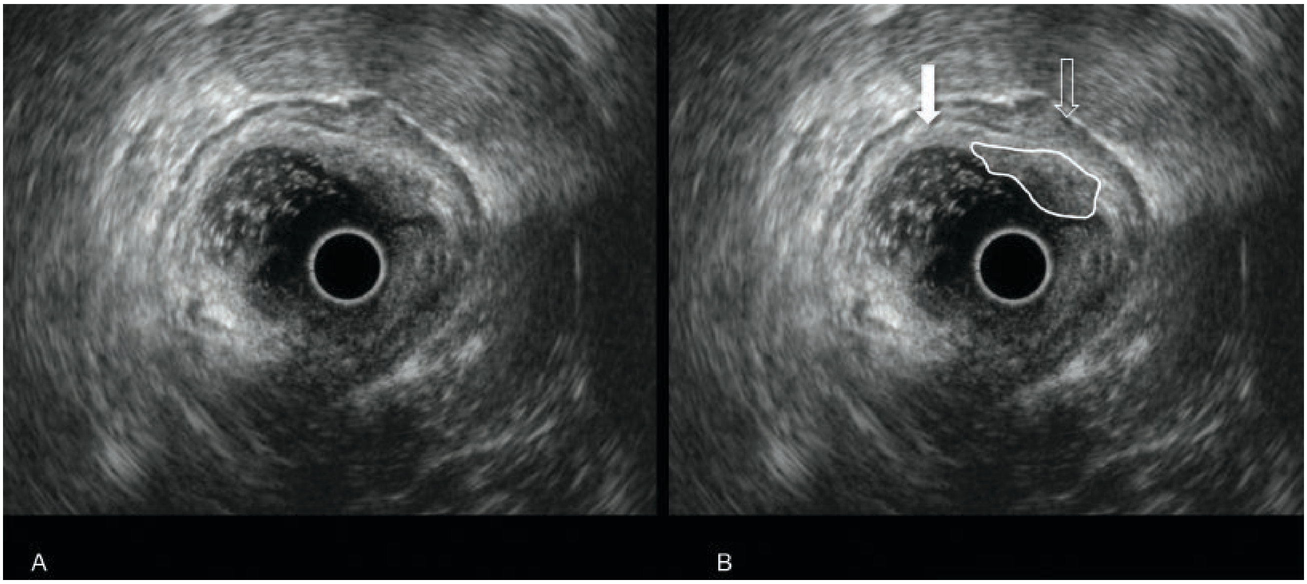

Figure 6 (A) Endorectal ultrasonographic image of a T1 tumor (outlined in (B)) invading the submucosa (bright, hyperechoic band illustrated with solid arrow) but not muscularis propria (hypoechoic/dark line, open arrow). Image courtesy of Dr Ed Godfrey, Cambridge University Hospitals.

(Kikuchi et al. 1995) is not possible. Moreover, endorectal ultrasound is operator-dependent with reduced accuracy for assessing more advanced tumors and nodal stage (Garcia-Aguilar et al. 2002). Endorectal ultrasound constitutes a useful adjunct for surgical planning and identifying rectal cancer eligible for transanal endoscopic microsurgery (TEMS) or transanal minimally invasive surgery (TAMIS). Its optimal accuracy seems to be when cancer is located 3-6 cm from the anal verge (Ren et al. 2018).

In rectal cancer, T3 stage is synonymous with tumor extension into the mesorectum and/or into the intersphincteric plane (for low rectal cancer) (Tapan et al. 2014). This translates on MRI to tumor signal extending into the perirectal fat with a rounded or nodular advancing margin and in continuity with the intramural portion of the tumor. The muscularis propria often has an irregular corrugated appearance in the absence of tumor and interruptions of this outer layer may occur normally due to penetrating blood vessels. Therefore, irregularity or disruption of the low signal muscularis propria itself is not sufficient to diagnose T3 disease. Spiculations within the mesorectal fat adjacent to the tumor are not necessarily a manifestation of extramural tumor spread, given that tumors may elicit a desmoplastic response or cause perivascular cuffing of the penetrating vessels. Nor can MRI reliably differentiate T2 from early T3 tumors, however this distinction is not clinically important as it will not generally affect the choice of treatment modality. T3 stage can be further divided into substage depending on the depth of invasion beyond the muscularis propria. An invasion into the mesorectum <5 mm is classified as mrT3a, and an invasion >5 mm as mrT3b (Zinicola et al. 2017). Alternatively, the subclassification can be as follows: mrT3a (<1 mm), mrT3b (1-5 mm), mrT3c (6-15 mm) and mrT3d (>15 mm) (Glynne-Jones et al. 2017) (Figures 7 and 8). This subclassification has prognostic value, as it also indirectly indicates the distance of

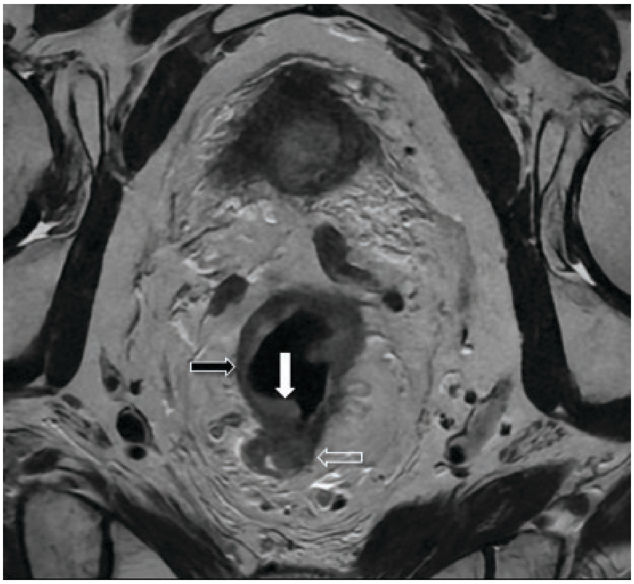

Figure 7 Axial oblique T2-weighted MR image of a T3a mid rectal tumor extending to 5–9 o'clock (solid white arrow). Muscularis propria is visible as a hypointense (dark) band (black arrow). Early soft tissue extension beyond muscularis propria by 1 mm is in keeping with T3a disease (open white arrow).

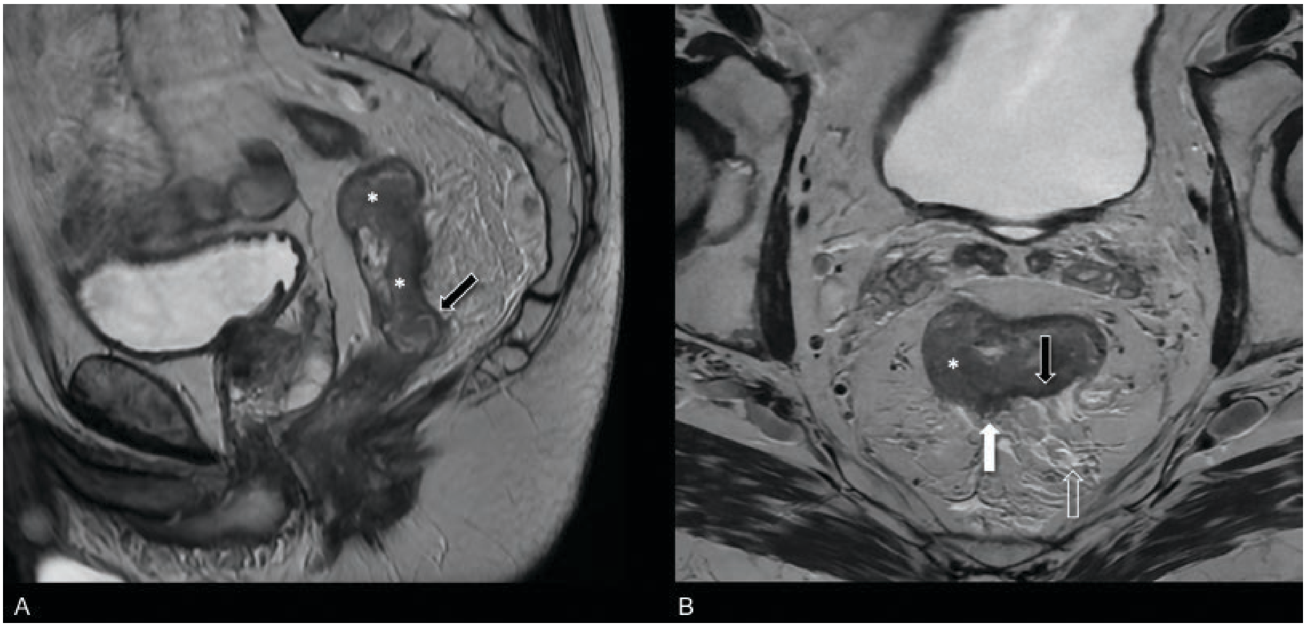

Figure 8 Sagittal (A) and axial oblique (B) T2-weighted MR image of a cT3b mid rectal tumor extending from 3–9 o'clock in the axial plane (asterisk). Muscularis propria is visible as a hypointense (dark) band (black arrow). Irregular tissue extending into the mesorectal fat by 6 mm is consistent with T3c disease (solid white arrow). More marked hyperintensity within the mesorectal fat represents edema (open arrow).

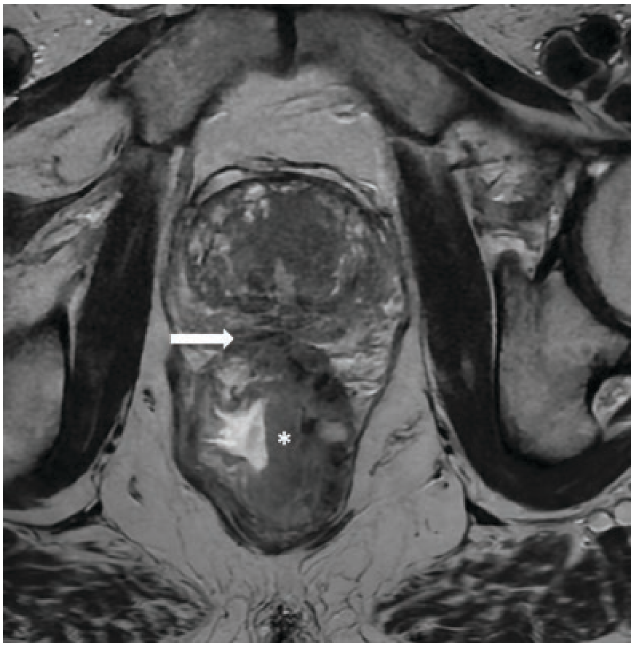

Figure 9 Locally advanced, T4b tumor. Axial T2-weighted MR image demonstrates a semi-annular tumor extending from 12–7 o'clock (asterisk) with extension anteriorly through the prostatic capsule (white arrow).

the tumor from the CRM (Merkel et al. 2001), and therefore the surgical margin in case of planned surgery with TME.

Finally, tumor extension into adjacent organs, pelvic sidewall or peritoneal reflection represents T4 disease (Figure 9). Tumor invasion beyond the intersphincteric plane into the external anal sphincter also represents T4 stage (Tapan et al. 2014). This corresponds to locally advanced rectal cancer, which is defined as cancer that is predicted by MRI to require an extended surgical resection beyond the TME plane to achieve a resection specimen with a pathologically clear resection margin (R0) (Beyond 2013).

Distance from the Anal Verge

Rectal cancer is usually classified as high rectal cancer (10–15 cm from the anal verge), mid rectal cancer (5–10 cm from the anal verge) and low rectal cancer (<5 cm from the anal verge) (Glynne-Jones et al. 2017). More recently, low rectal cancer was defined as a cancer with its lower edge at or below the origin of the levator muscles at the pelvic side-wall based on MRI (Salerno et al. 2006). The tumor's distance to the anal verge is assessed by a combination of digital rectal examination, rigid rectoscopy and pelvic MRI.

Estimating the precise location of rectal cancer is of crucial importance for therapeutic management. For instance, high rectal cancer (defined as >12cm from the anal verge and/or above the peritoneal reflection) may not require neo-adjuvant treatment in some countries and patients can benefit from anterior resection with partial mesorectal excision, likely without the need for a stoma. Mid and low rectal cancers, however, should be appropriately staged and consideration given for neoadjuvant (chemo)radiotherapy and followed by surgery with low anterior resection including TME if not entered into a "watch and wait" program.

A key question is whether to preserve the sphincters or not. If a stapling device can be safely applied at a distance below the lower edge of the tumor and an anastomosis performed above the sphincters (even if it involves a disconnection from the perineal approach and intersphincteric dissection), the sphincters (sometimes only the external sphincter) can be preserved. If not, and for example if the sphincter(s) are involved, an abdomino-perineal excision of the rectum (APER) should be performed. In addition to the anatomical findings, a patient may choose a stoma rather than a restorative procedure, but this is outside of the scope of this chapter.

Circumferential Resection Margin (CRM)

The circumferential resection margin (CRM) at the level of the mesorectum is represented by the mesorectal fascia (MRF), which surrounds the mesorectum. At MRI the MRF is identified as a thin low signal intensity linear structure encompassing the mesorectum. The tumor may directly spread to the MRF or may be present within lymph nodes, veins, lymphatics or as tumor deposits (Langman et al. 2017). Once identified, the presence of tumor close to the MRF may imply a threatened margin, which is usually defined as being within 1 mm (Figure 10). The prevalence of threatened MRF during staging MRI was estimated to be 13.2% (Group MS 2006). Involvement of the CRM constitutes an important risk factor for increased five-year incidence of local recurrence and distant metastases, and decreased five-year disease-free survival and overall survival (Detering et al. 2021). Therefore, if the CRM is threatened based on preoperative staging, the tumor is considered as locally advanced and neoadjuvant chemoradiotherapy should be proposed (Beyond 2013; Glynne-Jones et al., 2017). Of note, the nature of CRM involvement may influence oncological outcomes. For instance, some evidence indicates that patients with a MRF threatened by a lymph node have better oncological outcomes than patients with a MRF threatened by the primary tumor, which may be similar to the outcomes of patients with non-threatened MRF, notably in terms of local recurrence (Birbeck et al. 2002; Nagtegaal et al. 2002; Patel et al. 2019; Sao Juliao and Perez 2019; Smith et al. 2022; Suarez et al. 2018).

In the upper rectum, the anterior wall is covered by peritoneum, rather than mesorectum. Identification of the peritoneal reflection is important as peritoneal involvement by tumor represents T4a disease. Although the peritoneal reflection is a variable structure, it may be identified on the sagittal

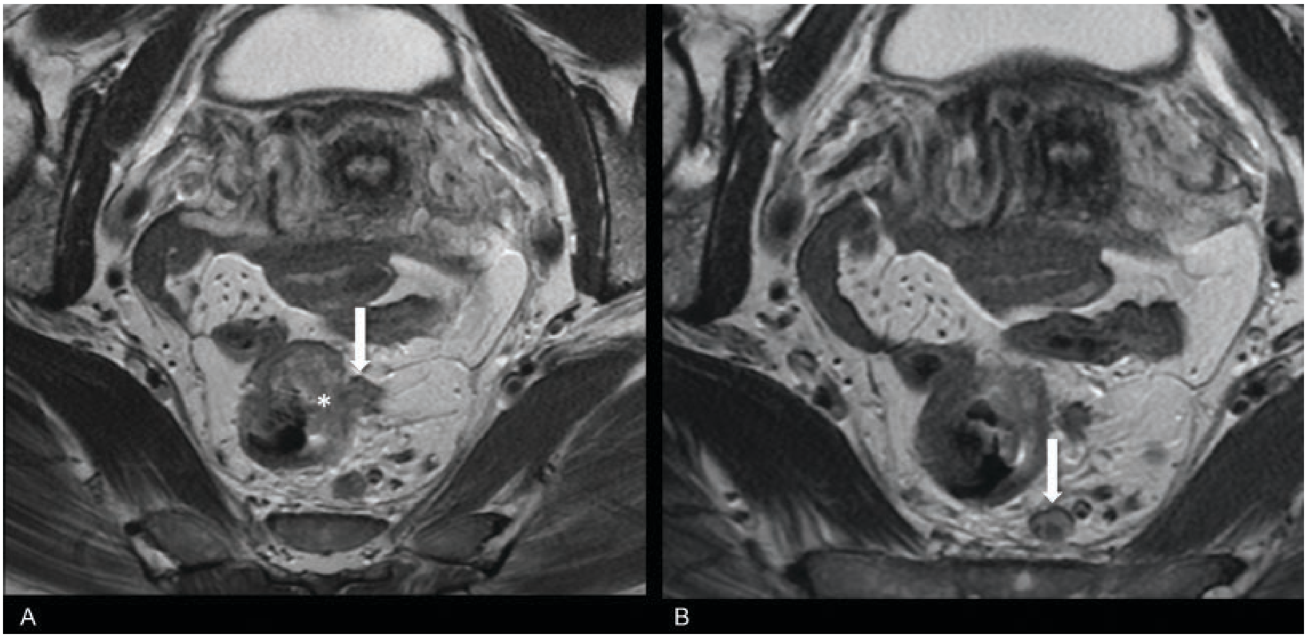

Figure 10 (A) Mesorectal fascia threatened at 2 o'clock (white arrow) by extension of a T3c semi-annular tumor (asterisk). (B) The fascia is also threatened at 6 o'clock by an enlarged and heterogeneous signal intensity node with malignant features (arrow).

images as a low signal intensity structure passing over the urinary bladder, which passes posteriorly to its point of attachment to the rectum.

In the lower rectum, the mesorectal plane is replaced by the intersphincteric plane. Invasion into the intersphincteric plane is considered as T3 disease, whereas invasion of the external anal sphincter or within 1 mm of the levator ani is considered as T4 disease (Santiago et al. 2020; Tapan et al. 2014) and may require extralevator abdomino-perineal excision (ELAPE) or a more extended procedure.

Vascular Invasion

In addition to direct extension, tumor may invade along blood vessel and lymphatics. Extramural venous invasion (EMVI) is present in up to one third of patients with rectal cancer (Siddiqui et al., 2017) and was identified as a strong predictor of disease-free survival (Gu et al. 2019) and both synchronous and metachronous metastases (Siddiqui et al. 2017). EMVI can be detected by CT but is better assessed by MRI. On thin-section MRI, extramural venous invasion (EMVI) by tumor can be readily identified and is demonstrated as serpiginous or tubular extension of tumor beyond the muscle coat (Figure 11). Sensitivity of MRI for detection of EMVI ranges between 50% to 83% (Brown et al. 2003; Zhang et al. 2018). A score to allow prediction of the presence of EMVI on histology based on MRI criteria has been developed (Smith et al. 2008)

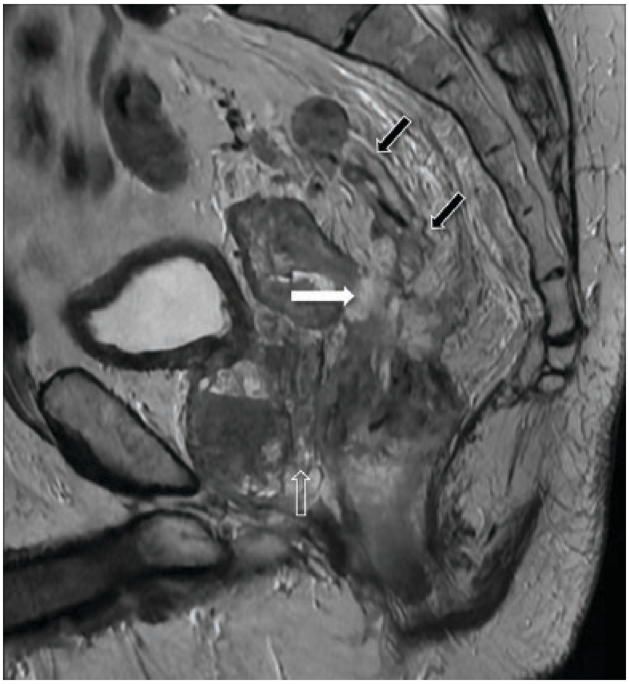

Figure 11 EMVI. Sagittal T2-weighted MR image of a bulky locally advanced mucinous tumor of the mid rectum (solid white arrow) with invasion into the prostate anteriorly (open arrow). Extensive mucinous tumor invasion (EMVI) of the superior rectal vein is clearly visible (black arrows).

Assessing Lymph Nodes (N)

As with colonic cancer, CT can only use size as a criterion for nodal involvement by tumor and as such suffers the same limitations. However, given the improved ability of MRI to resolve nodal morphology, further criteria have been developed. A wide variety of suggested cut-off values have been suggested for lymph node size ranging from 3 to 10 mm, with variable sensitivities and specificities. Other criteria based on the morphology of the node have therefore been developed. An irregular or indistinct border has consistently been shown to be a specific marker of likely lymph node positivity. Similarly, an irregular or heterogeneous signal from within the node also correlates with likely nodal positivity (Kim et al. 2004). Such criteria are independent of nodal size but when combined can increase the sensitivity and specificity of nodal staging to 90% (Brown 2005). However, imaging is unable to determine the presence of micrometastases (tumor deposits around 1–2 mm) within individual nodes.

Local nodes are located within the mesorectum. As with colonic cancer, the second group of nodes is related to the arterial blood supply. However, the rectum receives supply both from the inferior mesenteric artery and the internal iliac artery, via branches of the pudendal artery. Therefore, it is possible for nodal metastases to occur outside the mesorectum along the internal iliac chain with lateral spread to the pelvic sidewall or retroperitoneum (Figures 10 and 12).

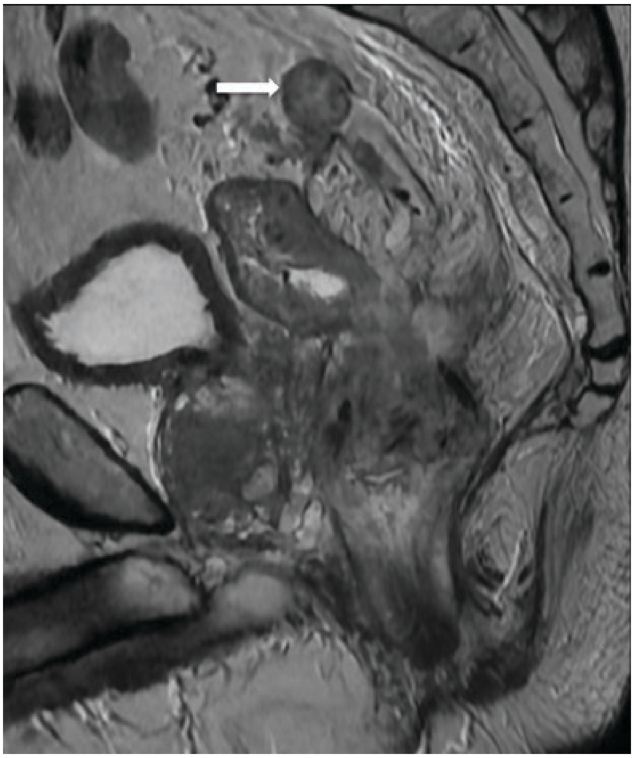

Figure 12 Same patient as in Figure 11. Large, heterogeneous signal intensity lymph node with an irregular border within the presacral space, consistent with metastasis. The node is in continuity with EMVI as demonstrated in Figure 11.

Colorectal Cancer Metastases

Recommended Imaging

Tumor cells can spread to distant organs to cause metastatic disease. This can occur through the hematogenous route, the lymphatic route or the transcoelomic route. At primary presentation of colorectal cancer, 17.6% of patients have metastasis, which defines stage IV disease (Moghadamyeghaneh et al. 2016). The most common site of metastasis are the liver (70%), the lungs (24%), distant lymph nodes (16%) and the peritoneum (15%) (Holch et al. 2017).

Recommended imaging looking for potential metastases of colorectal cancer includes CT of the chest, abdomen and pelvis, which provides a first assessment of central lymph nodes, liver and chest (Van Cutsem et al. 2016). CT has a sensitivity and specificity of 85% and 98% respectively for M-staging in colorectal cancer (Leufkens et al. 2011). Optimal detection of liver metastases requires intravenous contrast and scanning in the portal venous phase of enhancement. When metastatic disease is shown or suspected, the diagnostic management is then tailored to the patient and potential therapeutic strategy in a stepwise approach with imaging guided according to the potentially affected organs (Van Cutsem et al. 2016).

PET-CT is not routinely performed and should be reserved for decision-making in patients with stage IV disease (to look for additional sites of metastasis) and also in patients with normal staging CT but at high risk of metastatic disease, for example in case of extensive EMVI or high CEA (Glynne-Jones et al. 2017).

Liver Metastases

The liver is the most common site of metastatic disease in patients suffering from colorectal cancer. Optimal imaging is key to evaluate the potential resectability of metastases, which can be performed either by surgery or ablative treatments, such as thermal devices (radiofrequency ablation, cryoablation, microwave ablation), non-thermal devices (brachytherapy electroporation, external body radiotherapy with high-precision radiation therapy), embolic devices (selective internal radiation therapy (SIRT), transarterial chemoembolization (TACE)) or local chemotherapy (Van Cutsem et al. 2016). Usual indications for resection include the possibility to completely remove the liver disease (R0) while preserving an adequate future liver remnant (FLR) without concomitant unresectable extrahepatic disease (Adam et al. 2012; Van Cutsem et al. 2016).

At CT, liver metastases usually appear as lesions of decreased attenuation compared to the liver parenchyma. In the event of mucinous primary tumors, differentiation of cystic metastases from simple cysts may be difficult and is a recognized pitfall. Contrast-enhanced MRI is superior to contrast-enhanced CT for the detection of lesions above and below 1 cm in diameter (Figure 13). However, for colorectal cancer, it is not sufficient to simply diagnose the presence of metastatic disease within the

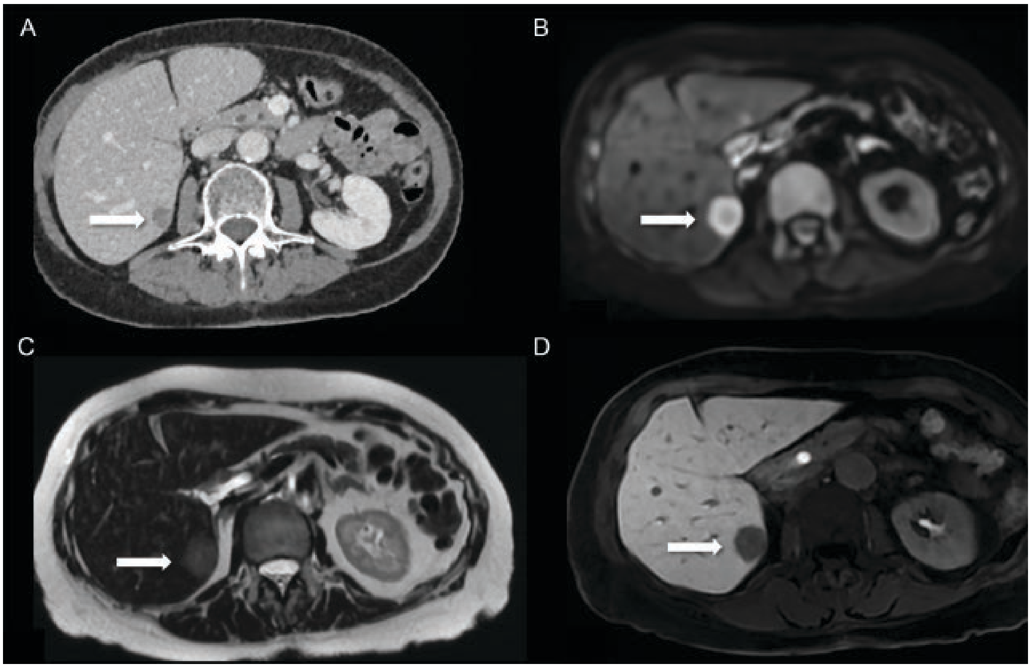

Figure 13 Enlarging liver metastasis. (A) Portal venous phase axial CT image demonstrates a hypoenhancing lesion within segment 7 (arrow), which subsequently enlarges in the interval prior to MR imaging. (B) Diffusion weighted MR image demonstrating the metastasis as a high signal, diffusion-restricting lesion which is hyperintense on T2-weighted imaging (C). Hepatobiliary contrast medium is taken up by normal liver parenchyma but not the metastasis, which appears as a hypointense (dark) lesion in (D).

liver. If the potential treatment is surgical resection, then it is necessary to detect all lesions and also to characterize their location. As a result both MRI and PET-CT are performed, the latter also enabling the identification of unsuspected extrahepatic metastatic disease (Adam et al. 2012; Bipat et al. 2005) although with reduced sensitivity for the detection of metabolically active deposits less than 1 cm in size or the detection of mucinous metastases. As a result, liver MRI is also indicated, while PET-CT may detect extrahepatic metastatic disease in up to 29% of patients considered for surgery, hence altering decision-making (Khan et al. 2006). For instance, metastasectomy was shown to improve cancer-specific survival in patients with liver metastases, but not in patients with lung metastases or synchronous lung and liver metastases (Siebenhuner et al. 2020).

Peritoneal Metastases

Synchronous and metachronous peritoneal metastases are present in 8.3% of patients with colorectal cancer (Segelman et al. 2012) (Figure 14). Of these patients, only 3% of patients are potentially eligible for surgery, which consists of cytoreductive surgery (CR) with hyperthermic intra-peritoneal chemotherapy (HIPEC) or pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with a Sugarbaker's peritoneal carcinomatosis index (PCI) <20 and no extra-peritoneal metastases (as verified by PET-CT). Therefore, diagnosing the presence of peritoneal metastases and characterizing their number and size is key for optimal surgical management and avoiding potentially unnecessary surgery. Unfortunately, pre-operative imaging techniques have poor sensitivity for diagnosing peritoneal disease. For instance, CT has a sensitivity ranging between 60 to 76% (de Bree et al. 2004; Marin et al. 2010) which varies according to the location of the metastases and their diameter. Its sensitivity further drops to 43% for lesions of a diameter smaller than 0.5 cm (Marin et al. 2010). Sensitivity of MRI has previously been similar to CT. However improved techniques – in particular diffusion-weighted imaging – have allowed its sensitivity to reach 84% with the better detection of smaller metastases (Low et al. 1997). Adding PET sequences does not seem to increase the diagnostic accuracy of pre-operative imaging techniques (Elekonawo et al. 2020). In the United Kingdom, these patients are still discussed routinely with the nominated national referral centers for peritoneal malignancy. In order to compensate for the low sensitivity of imaging techniques, patients with T4 colorectal cancer may benefit from laparoscopy for early detection of metachronous peritoneal carcinomatosis (Bastiaenen et al. 2019).

Lateral Pelvic Sidewall Lymph Nodes

Mid and low rectal cancers below the peritoneal reflection may metastasize to lateral pelvic sidewall lymph nodes, such as the internal iliac nodes, common iliac nodes, obturator nodes, and external iliac nodes (Bell et al. 2009). The prevalence of lateral pelvic sidewall lymph node metastases in patients with mid/low

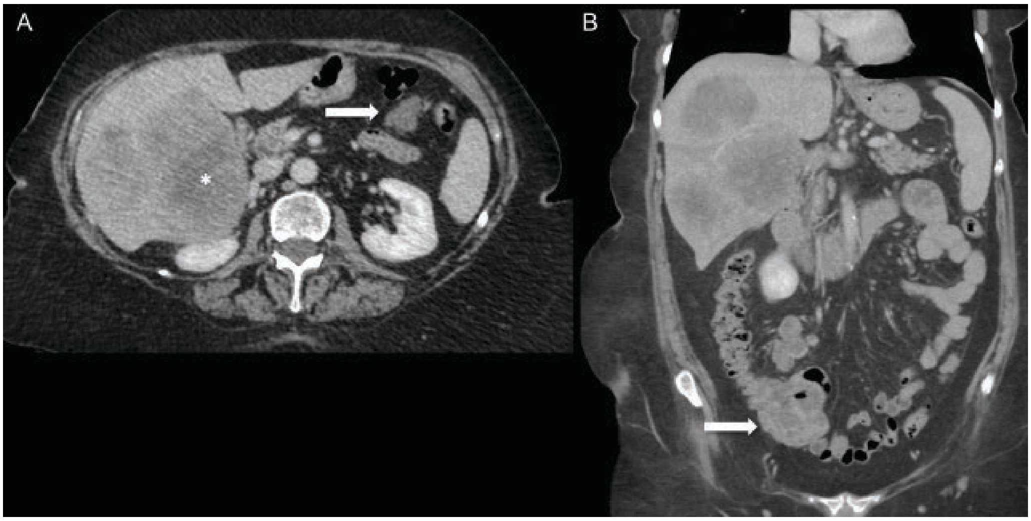

Figure 14 (A) Axial CT image demonstrating a large hepatic metastasis (asterisk) with peritoneal deposit adjacent to the jejunum and splenic flexure (white arrow). (B) Coronal MPR image demonstrating the cecal primary tumor.

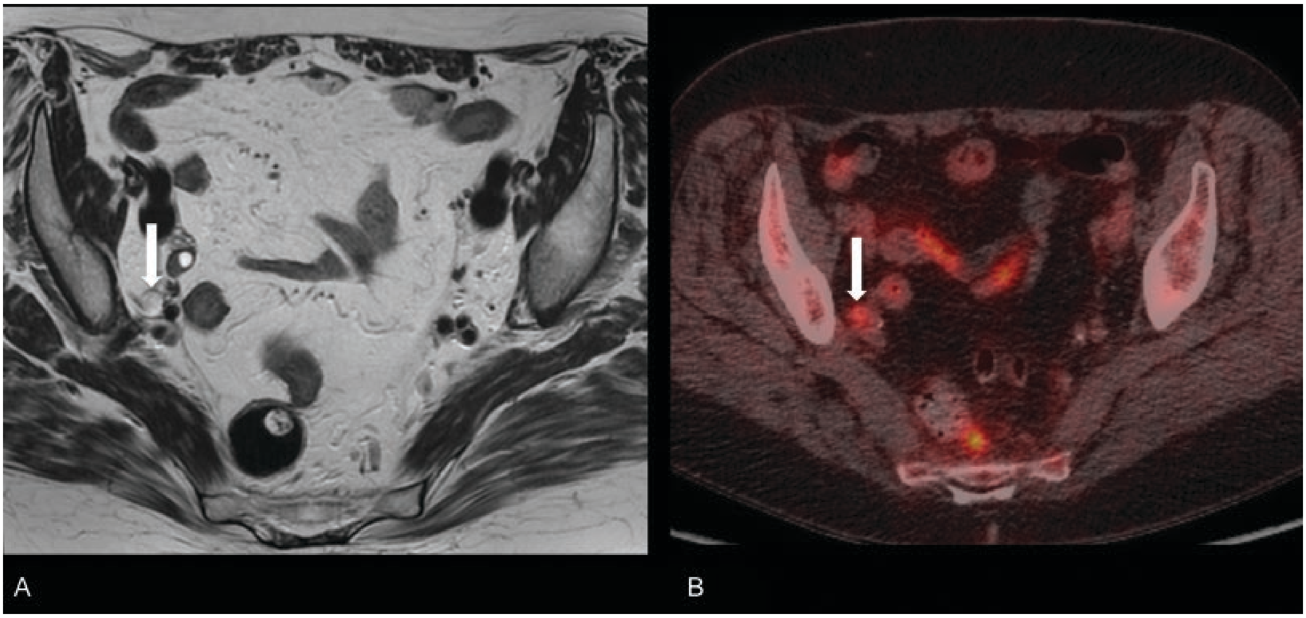

Figure 15 Metastatic lateral pelvic sidewall node. (A) Axial T2-weighted MR image demonstrates a high signal enlarged sidewall node adjacent to internal iliac vessels on the right, with signal characteristics consistent with a known mucinous primary (not shown). (B) 18F-fluorodeoxyglucose (18F-FDG) PET-CT fused axial image confirms avidity within the node, in keeping with metastatic disease.

rectal cancer is estimated to be around 17% (Christou et al. 2021) and is inversely proportional to tumor height (Ueno et al. 2005). Involvement of lateral pelvic sidewall lymph nodes constitutes a cause of recurrence in patients treated with preoperative chemoradiotherapy and rectal resection (Kim et al. 2008). Therefore, identifying these lateral pelvic sidewall lymph nodes at risk of lymph node metastases in the pre-operative setting is key for optimal multidisciplinary treatment. These nodes can be identified using CT, MRI, PET-CT or PET-MRI (Figure 15).

When using definitive histopathological analysis as a gold-standard, MRI has a sensitivity and specificity of 68.6% and 79.7% respectively for detecting lateral pelvic sidewall lymph nodes (with a cutoff axis of 5 mm) (Ogawa et al. 2016). If uncertainty remains the addition of PET, combined with either CT or MRI, may increase sensitivity. For instance, the metabolic tumor volume of the primary tumor and the maximum standardized uptake value (SUV) of suspected lymph nodes were demonstrated to be independent predictive factors for nodal metastases (Kim et al. 2019).

In Western countries, suspected involvement of these nodes will constitute an indication for chemoradiotherapy with or without a radiotherapy boost (Glynne-Jones et al. 2017). In case of absence or partial response after neoadjuvant treatment, the therapeutic strategy varies between radiotherapy boost to surgical excision of the rectum with lateral lymph node dissection (Hazen et al. 2021). Restaging MRI should be performed as it allows identification of lymph nodes at higher risk of recurrence (those with short axes of ≥0.5 cm) (Malakorn et al. 2019; Ogura et al. 2019). In Asia, routine lateral lymph node dissection is the preferred approach and can be performed unilaterally or bilaterally (Kanemitsu et al. 2017). Ongoing controversy exists regarding treatments for suspicious lateral pelvic side wall lymph nodes and indications for lateral lymph node dissection. Some authors recommend a selective approach (Kim et al. 2020).

Key Take Home Messages

Pre-operative imaging of colorectal cancer is key to assess the local and distant extents of the disease and to exclude synchronous cancer, with the objective of determining surgical resectability and eventual need for neo-adjuvant therapy. The three components of the clinical TNM stage should be assessed: the T(umor) stage, the N(odal) stage and the M(etastasis) stage. Imaging of colon cancer relies on CT of the chest, abdomen and pelvis, associated with a complete colonoscopy. Imaging of rectal cancer relies on the same modalities, but optimal assessment of local extension requires the addition of pelvic MRI. Pelvic MRI has to be reported according to a standardized form which provides the surgeon with the required minimal information for surgical planning. In case of suspected metastasis, optimal imaging has to be tailored to the patient.

Areas for Further Research

Although imaging and staging of colorectal cancer has seen major improvements over the last decade, the field deserves further improvements. Of note, more sensitive and specific methods for detecting peritoneal carcinomatosis and metastatic lateral lymph nodes are awaited. Moreover, assessment of tumor response to neo-adjuvant treatment could be improved, notably by the use of functional imaging methods. And finally, molecular imaging using radio-labeled antibodies could potentially assess the bio-distribution and bio-availability of potential targets for immunotherapy (Van Cutsem et al. 2016).

References

Adam, R., De Gramont, A., Figueras, J. et al. (2012). The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 17: 1225–1239.

Alsabilah, J.F., Razvi, S.A., Albandar, M.H. et al. (2017). Intraoperative archive of right colonic vascular variability aids central vascular ligation and redefines gastrocolic trunk of henle variants. *Dis Colon Rectum* 60: 22–29.

Argiles, G., Tabernero, J., Labianca, R. et al. (2020). Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 31: 1291–1305.

Bass, G., Fleming, C., Conneely, J. et al. (2009). Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. *Dis Colon Rectum* 52: 678–684.

Bastiaenen, V.P., Klaver, C.E.L., Kok, N.F.M. et al. (2019). Second and third look laparoscopy in pT4 colon cancer patients for early detection of peritoneal metastases; the COLOPEC 2 randomized multicentre trial. *BMC Cancer* 19: 254.

Bell, S., Sasaki, J., Sinclair, G. et al. (2009). Understanding the anatomy of lymphatic drainage and the use of blue-dye mapping to determine the extent of lymphadenectomy in rectal cancer surgery: unresolved issues. *Colorectal Dis* 11: 443–449.

Beyond, T.M.E.C. (2013). Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg* 100: E1–33.

Bipat, S., van Leeuwen, M.S., Comans, E.F. et al. (2005). Colorectal liver metastases: CT, MR imaging, and PET for diagnosis–meta-analysis. *Radiology* 237: 123–131.

Birbeck, K.F., Macklin, C.P., Tiffin, N.J. et al. (2002). Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 235: 449–457.

Body, A., Prenen, H., Latham, S. et al. (2021). The role of neoadjuvant chemotherapy in locally advanced colon cancer. *Cancer Manag Res* 13: 2567–2579.

Brown, G. (2005). Thin section MRI in multidisciplinary pre-operative decision making for patients with rectal cancer. *Br J Radiol* 78 (Spec No 2): S117–27.

Brown, G., Radcliffe, A.G., Newcombe, R.G. et al. (2003). Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. *Br J Surg* 90: 355–364.

Brown, G., Richards, C.J., Newcombe, R.G. et al. (1999). Rectal carcinoma: thin-section MR imaging for staging in 28 patients. *Radiology* 211: 215–222.

Cancer KSGfR (2017). Essential items for structured reporting of rectal cancer MRI: 2016 consensus recommendation from the Korean society of abdominal radiology. *Korean J Radiol* 18: 132–151.

Christou, N., Meyer, J., Combescure, C. et al. (2021). Prevalence of metastatic lateral lymph nodes in Asian patients with lateral lymph node dissection for rectal cancer: a meta-analysis. *World J Surg* 45: 1537–1547.

Davies, J., Chew, C., Bromham, N. et al. (2022). NICE 2020 guideline for the management of colorectal cancer. *Lancet Oncol* 23: e247.

de Bree, E., Koops, W., Kroger, R. et al. (2004). Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 86: 64–73.

Detering, R., Rutgers, M.L.W., Bemelman, W.A. et al. (2021). Prognostic importance of circumferential resection margin in the era of evolving surgical and multidisciplinary treatment of rectal cancer: a systematic review and meta-analysis. *Surgery* 170 (2): 412–431.

Dighe, S., Purkayastha, S., Swift, I. et al. (2010). Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. *Clin Radiol* 65: 708–719.

Elekonawo, F.M.K., Starremans, B., Laurens, S.T. et al. (2020). Can [(18)F] F-FDG PET/CT be used to assess the pre-operative extent of peritoneal carcinomatosis in patients with colorectal cancer? *Abdom Radiol (NY)* 45: 301–306.

Elibol, F.D., Obuz, F., Sokmen, S. et al. (2016). The role of multidetector CT in local staging and evaluation of retroperitoneal surgical margin involvement in colon cancer. *Diagn Interv Radiol* 22: 5–12.

Flor, N., Mezzanzanica, M., Rigamonti, P. et al. (2013). Contrast-enhanced computed tomography colonography in preoperative distinction between T1-T2 and T3-T4 staging of colon cancer. *Acad Radiol* 20: 590–595.

Garcia-Aguilar, J., Pollack, J., Lee, S.H. et al. (2002). Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. *Dis Colon Rectum* 45: 10–15.

Glynne-Jones, R., Wyrwicz, L., Tiret, E. et al. (2017). Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 28: iv22–iv40.

Graser, A., Stieber, P., Nagel, D. et al. (2009). Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. *Gut* 58: 241–248.

Group MS (2006). Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 333: 779.

Gu, C., Yang, X., Zhang, X. et al. (2019). The prognostic significance of MRI-detected extramural venous invasion, mesorectal extension, and lymph node status in clinical T3 mid-low rectal cancer. *Sci Rep* 9: 12523.

Gupta, N.A., Mahajan, S., Sumankumar, A. et al. (2020). Impact of a standardized reporting format on the quality of MRI reports for rectal cancer staging. *Indian J Radiol Imaging* 30: 7–12.

Hazen, S.M., Sluckin, T., Beets, G. et al. (2021). Current practices concerning the assessment and treatment of lateral lymph nodes in low rectal cancer: a survey among colorectal surgeons in The Netherlands. *Acta Chir Belg* 1–9.

Holch, J.W., Demmer, M., Lamersdorf, C. et al. (2017). Pattern and dynamics of distant metastases in metastatic colorectal cancer. *Visc Med* 33: 70–75.

Japanese Society for Cancer of the C, Rectum (2019). Japanese classification of colorectal, appendiceal, and anal carcinoma: the 3D English edition [Secondary Publication]. *J Anus Rectum Colon* 3: 175–195.

Kanemitsu, Y., Komori, K., Shida, D. et al. (2017). Potential impact of lateral lymph node dissection (LLND) for low rectal cancer on prognoses and local control: a comparison of 2 high-volume centers in Japan that employ different policies concerning LLND. *Surgery* 162: 303–314.

Khan, S., Tan, Y.M., John, A. et al. (2006). An audit of fusion CT-PET in the management of colorectal liver metastases. *Eur J Surg Oncol* 32: 564–567.

Kikuchi, R., Takano, M., Takagi, K. et al. (1995). Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum* 38: 1286–1295.

Kim, J.H., Beets, G.L., Kim, M.J. et al. (2004). High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? *Eur J Radiol* 52: 78–83.

Kim, M.J., Chang, G.J., Lim, H.K. et al. (2020). Oncological impact of lateral lymph node dissection after preoperative chemoradiotherapy in patients with rectal cancer. *Ann Surg Oncol* 27: 3525–3533.

Kim, S.H., Song, B.I., Kim, B.W. et al. (2019). Predictive value of [(18)F] FDG PET/CT for lymph node metastasis in rectal cancer. *Sci Rep* 9: 4979.

Kim, T.H., Jeong, S.Y., Choi, D.H. et al. (2008). Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 15: 729–737.

Kuzu, M.A., Ismail, E., Celik, S. et al. (2017). Variations in the vascular anatomy of the right colon and implications for right-sided colon surgery. *Dis Colon Rectum* 60: 290–298.

Langman, G., Loughrey, M., Shepherd, N. et al. (2017). Association of Coloproctology of Great Britain & Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017) - pathology standards and datasets. *Colorectal Dis* 19 (Suppl 1): 74–81.

Latournerie, M., Jooste, V., Cottet, V. et al. (2008). Epidemiology and prognosis of synchronous colorectal cancers. *Br J Surg* 95: 1528–1533.

Leufkens, A.M., van den Bosch, M.A., van Leeuwen, M.S. et al. (2011). Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. *Scand J Gastroenterol* 46: 887–894.

Low, R.N., Barone, R.M., Lacey, C. et al. (1997). Peritoneal tumor: MR imaging with dilute oral barium and intravenous gadolinium-containing contrast agents compared with unenhanced MR imaging and CT. *Radiology* 204: 513–520.

Malakorn, S., Yang, Y., Bednarski, B.K. et al. (2019). Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? *Dis Colon Rectum* 62: 1158–1166.

Marin, D., Catalano, C., Baski, M. et al. (2010). 64-Section multi-detector row CT in the preoperative diagnosis of peritoneal carcinomatosis: correlation with histopathological findings. *Abdom Imaging* 35: 694–700.

Merkel, S., Mansmann, U., Siassi, M. et al. (2001). The prognostic inhomogeneity in pT3 rectal carcinomas. *Int J Colorectal Dis* 16: 298–304.

Moghadamyeghaneh, Z., Alizadeh, R.F., Phelan, M. et al. (2016). Trends in colorectal cancer admissions and stage at presentation: impact of screening. *Surg Endosc* 30: 3604–3610.

Mulder, S.A., Kranse, R., Damhuis, R.A. et al. (2011). Prevalence and prognosis of synchronous colorectal cancer: a Dutch population-based study. *Cancer Epidemiol* 35: 442–447.

Nagtegaal, I.D., Marijnen, C.A., Kranenbarg, E.K. et al. (2002). Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 26: 350–357.

NIfHaCE (NICE). (2020). Colorectal cancer: NICE guideline (NG151).

Nuernberg, D., Saftoiu, A., Barreiros, A.P. et al. (2019). EFSUMB recommendations for gastrointestinal ultrasound part 3: endorectal, endoanal and perineal ultrasound. *Ultrasound Int Open* 5: E34–E51.

Ogawa, S., Hida, J., Ike, H. et al. (2016). Selection of lymph node-positive cases based on perirectal and lateral pelvic lymph nodes using magnetic resonance imaging: study of the Japanese society for cancer of the colon and rectum. *Ann Surg Oncol* 23: 1187–1194.

Ogura, A., Konishi, T., Beets, G.L. et al. (2019). Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. *JAMA Surg* 154: e192172.

Patel, A., Green, N., Sarmah, P. et al. (2019). The clinical significance of a pathologically positive lymph node at the circumferential resection margin in rectal cancer. *Tech Coloproctol* 23: 151–159.

Plumb, A.A., Halligan, S., Nickerson, C. et al. (2014a). Use of CT colonography in the English bowel cancer screening programme. *Gut* 63: 964–973.

Plumb, A.A., Halligan, S., Pendse, D.A. et al. (2014b). Sensitivity and specificity of CT colonography for the detection of colonic neoplasia after positive faecal occult blood testing: systematic review and meta-analysis. *Eur Radiol* 24: 1049–1058.

Puli, S.R., Bechtold, M.L., Reddy, J.B. et al. (2009). How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. *Ann Surg Oncol* 16: 254–265.

Ren, Y., Ye, J., Wang, Y. et al. (2018). The optimal application of transrectal ultrasound in staging of rectal cancer following neoadjuvant therapy: a pragmatic study for accuracy investigation. *J Cancer* 9: 784–791.

Salerno, G., Sinnatamby, C., Branagan, G. et al. (2006). Defining the rectum: surgically, radiologically and anatomically. *Colorectal Dis* 8 (Suppl 3): 5–9.

Santiago, I., Figueiredo, N., Pares, O. et al. (2020). MRI of rectal cancer-relevant anatomy and staging key points. *Insights Imaging* 11: 100.

Sao Juliao, G.P. and Perez, R.O. (2019). The influence of metastatic lymph nodes at the circumferential resection margin of rectal cancer-Do these lymph nodes require any special attention? *Tech Coloproctol* 23: 81–82.

Segelman, J., Granath, F., Holm, T. et al. (2012). Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 99: 699–705.

Siddiqui, M.R.S., Simillis, C., Hunter, C. et al. (2017). A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer* 116: 1513–1519.

Siebenhuner, A.R., Guller, U., and Warschkow, R. (2020). Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases. *BMC Cancer* 20: 246.

Smith, H.G., Skovgaards, D.M., Chiranth, D. et al. (2022). The impact of subdivisions of microscopically positive (R1) margins on patterns of relapse in stage III colorectal cancer - A retrospective cohort study. *Colorectal Dis* 24 (7): 828–837.

Smith, N.J., Barbachano, Y., Norman, A.R. et al. (2008). Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg* 95: 229–236.

Smith, N.J., Bees, N., Barbachano, Y. et al. (2007). Preoperative computed tomography staging of nonmetastatic colon cancer predicts outcome: implications for clinical trials. *Br J Cancer* 96: 1030–1036.

Suarez, J., Goicoetxea, A., Gomez, M.L. et al. (2018). Impact of specific modes of circumferential resection margin involvement in rectal cancer local recurrence: a retrospective study. *J Surg Oncol* 118: 1122–1128.

Tapan, U., Ozbayrak, M., and Tatli, S. (2014). MRI in local staging of rectal cancer: an update. *Diagn Interv Radiol* 20: 390–398.

Ueno, M., Oya, M., Azekura, K. et al. (2005). Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. *Br J Surg* 92: 756–763.

Van Cutsem, E., Cervantes, A., Adam, R. et al. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27: 1386–1422.

Van Cutsem, E., Verheul, H.M., Flamen, P. et al. (2016). Imaging in colorectal cancer: progress and challenges for the clinicians. *Cancers (Basel)* 8.

Wang, X., Yuan, M., Mi, H. et al. (2020). The feasibility of differentiating colorectal cancer from normal and inflammatory thickening colon wall using CT texture analysis. *Sci Rep* 10: 6346.

Yamaoka, Y., Kinugasa, Y., Shiomi, A. et al. (2017). The distribution of lymph node metastases and their size in colon cancer. *Langenbecks Arch Surg* 402: 1213–1221.

Zhang, X.Y., Wang, S., Li, X.T. et al. (2018). MRI of extramural venous invasion in locally advanced rectal cancer: relationship to tumor recurrence and overall survival. *Radiology* 289: 677–685.

Zinicola, R., Pedrazzi, G., Haboubi, N. et al. (2017). The degree of extramural spread of T3 rectal cancer: an appeal to the American Joint Committee on Cancer. *Colorectal Dis* 19: 8–15.

Zorcolo, L., Fantola, G., Cabras, F. et al. (2009). Preoperative staging of patients with rectal tumors suitable for transanal endoscopic microsurgery (TEM): comparison of endorectal ultrasound and histopathologic findings. *Surg Endosc* 23: 1384–1389.

Surgery of Colorectal Cancer

Principles of Colorectal Surgery

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Key Take Home Messages

- In spite of various surgical techniques and approaches, the key tenets in oncologic colorectal surgery are adequate circumferential and longitudinal margins and lymphadenectomy.
- Colorectal surgeons tailor the approach to individual patient circumstances; in some cases, this leads to more minimally invasive surgery while other cases require more maximally invasive surgery.
- Emerging technologies all enable the colorectal surgeon to visualize the anatomy and planes better, and could enter widespread use to improve oncologic outcomes.

Introduction

Surgery remains the cornerstone in the treatment of colorectal cancer, and advances in surgical techniques have contributed to improvements in outcomes. The importance of surgery in the management of colorectal cancer is evident given that almost two-thirds of all patients diagnosed with colorectal cancer undergo some form of surgical intervention. This chapter first presents the established tenets of colorectal surgery, before discussing two key trends which have become commonplace in contemporary practice. The first being a trajectory toward more minimally invasive surgery. The second, diametrically opposite, pushes toward more aggressive and maximally invasive surgery. The balance between these two trends is intriguing, and the modern colorectal surgeon has become adept at applying these seemingly differing surgical philosophies depending on the nature of the cancer and patient. Finally, we explore future technologies which have the potential to shape colorectal surgical practice in the decades to come.

Principles of Gastrointestinal Surgery in Colorectal Cancer

Margins

Longitudinal surgical margins are critical in any oncologic surgery to ensure that microscopic tumor cells which may result in local recurrence are removed. Microscopically positive, or

R1 margins, are independently associated with metachronous systemic disease, as well as reduced three-year recurrence free survival (Schellenberg et al. 2022; Smith et al. 2022). The desire to remove more bowel to reduce recurrence needs to be balanced against the sacrifice of unnecessary bowel length. A study by Hashiguchi et al. demonstrated that there was no additional benefit in overall survival in resections extending more than 5 cm from the proximal or distal margin (Hashiguchi et al. 2011). These margins also impact on the extent of lymphadenectomy subtended by the resection, and margins <5 cm may be associated with understaging (Rørvig et al. 2014). The American Society of Colon and Rectal Surgeons (ASCRS) recommends a longitudinal resection margin of 5–7 cm (Vogel et al. 2022).

This may however be challenging to achieve in rectal cancer, given the need to preserve sphincter function, and ensure a safe anastomosis. In rectal cancer, a resection margin of 1–2 cm is therefore generally accepted, with the literature currently probing whether a sub centimeter margin might be safely performed. Among patients who received neoadjuvant chemoradiotherapy, resection margins <1 cm were associated with increased three-year local recurrence rates, and was a significant risk factor for local recurrence on multivariate analysis (Song et al. 2021). Another meta-analysis conversely showed that a resection margin of <1 cm did not result in increased risk of local recurrence, except in patients who received surgery alone. In this subgroup, the relative risk for local recurrence was 1.76 times higher in patients with a margin <1 cm, compared to patients with resection margin of 1 cm or more (Yan et al. 2022).

Lymphadenectomy

A minimal number of 12 lymph nodes harvested during surgery has traditionally been considered to be the cut-off for adequate staging of colorectal cancer (Amin et al. 2017), and this has also been used as a surgical quality indicator (Dillman et al. 2009). The origin of the number 12 can be traced to the 1990 World Congress of Gastroenterology in Sydney, where it was calculated that harvesting 12 lymph nodes would allow the pathologist to accurately stage a tumor as being N0 90% of the time (McDonald et al. 2012; Scott and Grace 1989). Since then, the use of 12 as an absolute cut-off has been controversial. Opponents of the use of an absolute cut-off argue that this fails to consider the effect of other factors which may impact on the lymph node harvest, such as age <60, or sidedness of the cancer (Shen et al. 2009). Furthermore, there is evidence that reduced lymph node harvest may not be an indicator for poor surgical technique, but rather, is a marker of reduced immune sensitivity and worse prognosis (Chan and Buczacki 2022; Lal et al. 2022). Nonetheless, 12 lymph nodes are considered to be the de facto minimal lymph node harvest in most surgical guidelines, and remains surgical dogma.

Surgical Procedures for Colorectal Cancer

There is mostly consensus regarding the operation of choice for cancers arising at different locations of the colon and rectum (Figure 1). These operations take into account the abovementioned

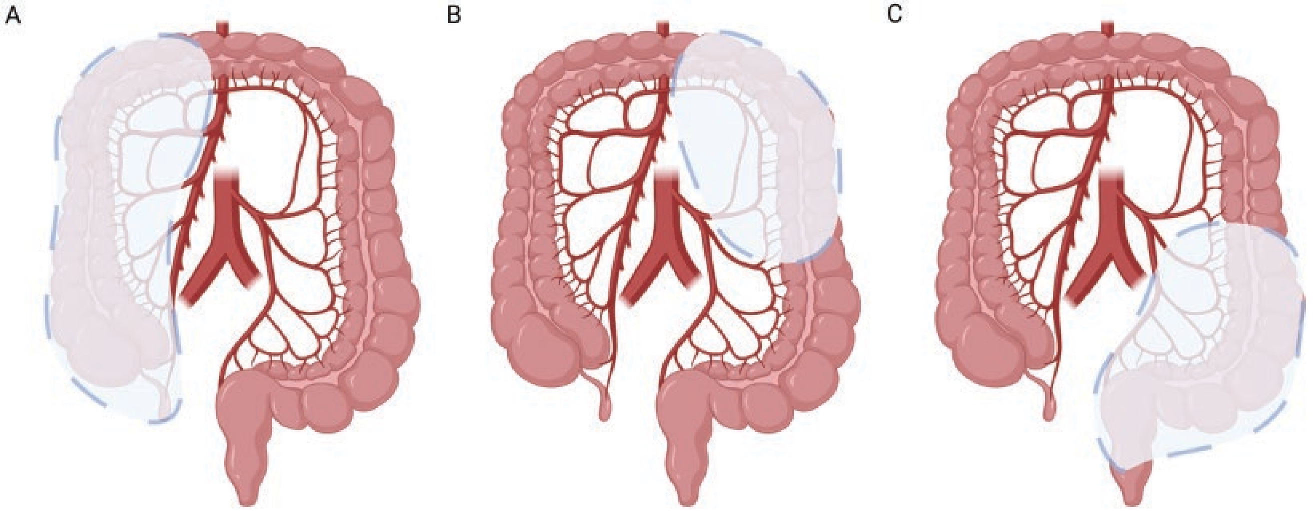

Figure 1 Colonic resections are determined based on the resected vascular pedicle. A. In a right hemicolectomy, the ileocolic vessels, a branch of the superior mesenteric bundle, are resected. The terminal ileum is anastomosed to the transverse colon. B. In a left hemicolectomy, the left colic vessels are resected and the transverse colon is anastomosed to the sigmoid colon. C. In an anterior resection, the inferior mesenteric vessels are resected, and the descending colon is anastomosed to the rectum. Created with biorender.com.

principles regarding margins and adequate lymphadenectomy. Tumors of the right colon are treated with a right hemicolectomy, while tumors of the left colon are treated with either a left hemicolectomy or an anterior resection. Low anterior resections are defined as those in which the anastomosis is made distal to the peritoneal reflection. An abdominal–perineal resection occurs when the anal sphincter has to be sacrificed based on the abovementioned oncologic principles.

There is however some controversy regarding cancers which arise at the splenic flexure. Some considerations of surgical choice in addition to the aforementioned surgical principles include this location being perfused by the terminal supply of both the superior and inferior mesenteric vessels, as well as the length of bowel and its impact on function beyond what is needed for oncologic clearance but instead to ensure a safe, tension-free bowel anastomosis. An analysis of short-term outcomes using the American College of Surgeons (ACS) NSQIP database showed no difference in lymph node yield between a segmental splenic flexure resection and a formal left hemicolectomy (Pang et al. 2022). Segmental resection however required a shorter operative time, and had equivalent postoperative morbidity. Another retrospective study compared the three main operations offered for cancers at the splenic flexure – extended right hemicolectomy, segmental splenic flexure colectomy, and left hemicolectomy (Manceau et al. 2022). Only extended right hemicolectomy resulted in a significantly higher lymph node yield, but at the expense of increased operative time and increased hospital length of stay. Notably, all three approaches did not result in differences in disease-free or overall survival. A trial designed specifically to address cancers at this challenging will remain difficult, given the paucity of splenic flexure cancers, and the number of variables which will need to be standardized to account for the multiple factors affecting surgical choice.

Minimally Invasive Surgery – Smaller Incisions to Scarless

Laparoscopic Colon and Rectal Surgery

In most elective settings, surgery for colorectal cancer is performed via a laparoscopic approach. In colon cancer, the benefits of the laparoscopic approach have been well established through multiple randomized controlled trials. The MRC CLASICC trial demonstrated equivalent short-term outcomes such as positive margin and complication rates between the open and laparoscopic approach (Guillou et al. 2005), as well as equivalent long-term outcomes such as overall survival, and recurrence rates over a follow-up period with a mean of five years (Green et al. 2013). Similar findings have been corroborated with other studies, all with the additional benefit of laparoscopic surgery requiring a smaller incision, and therefore leading to less pain, decreased opioid use, reduced hospital length-of-stay, and earlier return to premorbid function (Lacy et al. 2002; Clinical Outcomes of Surgical Therapy Study Group et al. 2004).

Trials with the aim of establishing the safety and oncologic efficacy of laparoscopic surgery in rectal cancer have also been performed. The COLOR II trial demonstrated no difference in short-term surgical outcomes (van der Pas et al. 2013), and equivalent rates of oncologic outcomes such as locoregional recurrence, disease-free survival and overall survival between patients who had undergone a laparoscopic or an open approach to surgery (Bonjer et al. 2015). Similar results have been observed in other trials performed over a diversity of geographic regions, such as the ACOSOG Z6051 in the United States (Fleshman et al. 2019), the COREAN trial in South Korea (Park et al. 2021) and randomized controlled trials performed in Hong Kong (Ng et al. 2014, 2009). Intriguingly, the ALaCart trial performed in Australasia however failed to prove noninferiority of the laparoscopic approach in terms of oncologic outcomes at median follow-up of 3.2 years, and the authors continue to await longer term results (Stevenson et al. 2019). Nonetheless, the evidence would suggest (with caution) that the laparoscopic approach is favorable in rectal cancer, as in colon cancer.

Robotic Surgery

The robotic approach to colorectal surgery has gained in prominence amongst surgeons in recent years, though it has not reached a level of acceptance achieved by the laparoscopic approach. Proponents of the robotic approach argue that the stable platform and decreased reliance on a competent assistance enable better dissection deep into the pelvis, as well as in circumstances which require precision, such as in lateral pelvic side wall lymph node dissection (Baek et al. 2013). Indeed, a randomized controlled trial performed in South Korea showed that the robotic approach achieved similar levels of total mesorectal excision (TME) quality, with similar results in terms of postoperative morbidity, return of bowel function, and quality of life scores (Kim et al. 2018). The ROLARR trial compared evaluated similar short-term outcomes. Notably, this study was powered to compare the rates of conversion to open approach as its primary endpoint, with secondary end-points including postoperative complications, circumferential resection margin positivity, and bladder and sexual function (Jayne et al. 2017). Given that the study showed no difference in the risk of conversion to the open approach, the authors were critical of the robotic approach, and did not deem it to be superior to laparoscopic surgery, particularly given the much-increased costs associated with robotic surgery. The surgical community eagerly awaits longer-term oncologic results from the trial.

Natural Orifice Approaches for Early Rectal Cancer

Early rectal cancers can be managed in a natural orifice approach as the risk of lymph node metastasis is often so limited as to not require lymphadenectomy. In the absence of lymphovascular invasion and non-poorly differentiated tumors, the risk of lymph node metastasis in pT1 cancers was found to be 7.5% only (Chang et al. 2012). pT2 lesions significantly increased this risk to 23.1%. For this reason, pT1 lesions in the absence of high-risk features can be considered adequately treated with local resection.

Transanal endoscopic microsurgical dissection (TEM) or transanal endoscopic microsurgery (TAMIS) are two different platforms with the aim of locally dissecting an early rectal cancer without the need for more radical surgical approaches. These two procedures are forms of natural orifice transluminal endoscopic surgery (NOTES), in which no surgical scar is made for removal of the lesion. Meta-analyses have confirmed that TEM is comparable to formal surgical resection for early rectal cancers. In patients who have undergone TEM compared with formal surgical resection for pT1 cancers, patients undergoing TEM reported lower surgical morbidity and mortality, and shorter hospital stays (Allaix et al. 2016). While Heintz et al. (Heintz et al. 1998) showed that patients with TEM had higher local recurrence rates, all studies have not shown that this translated into difference in long-term oncologic outcome (Heintz et al. 1998; Lee et al. 2003).

Maximally Invasive Surgery – beyond TME, CME, and Pelvic Exenteration

Total Mesorectal Excision (TME)

TME is unquestionably one of the key surgical techniques which significantly improved oncologic outcomes in rectal cancer. The principle of TME is that pararectal lymph nodes drain into the mesorectum, such that excision of this mesorectum leads to adequate lymphadenectomy. This technique therefore encompasses removal of the rectum together with its enveloping mesorectum, by sharp dissection along the visceral pelvic fascia, termed the "Holy Plane" (Heald 1988). Application of this technique ensures that cancer tissue is completely removed, and accords the patient the benefit of having a negative resection margin. Involvement of the resection margin with tumor is associated with a drastic increase in locoregional recurrence from 10% in uninvolved margins, to 78% in involved margins (Adam et al. 1994), and an increase in distal metastases from 12% to 40% (Wibe et al. 2002). Pathologic examination of the quality of TME is important as the quality of TME is correlated with recurrence rates. In patients who had an inadequate TME, recurrence was noted to be significant higher compared with patients who received a complete TME (Nagtegaal et al. 2002).

Transanal TME (TaTME) is a recent modification of the TME technique. In TaTME, the TME is performed transanally instead of trans-abdominally. This technique usually requires two surgical teams operating concurrently – one focusing on the trans-abdominal part of the surgery, while another dissects the TME plane by making a full-thickness incision through the anus distal to the cancer. Both teams "meet-up" on completion of the TME. One of the clear advantages of this approach is that the distal margin is always assured. Although some retrospective studies have consistently shown no difference in short-term surgical outcomes, and long-term oncologic outcomes [39–41], there has been significant concern regarding the technical challenges of this procedure and a pattern of multifocal local recurrence unique to TaTME (van Oostendorp et al. 2020). In Norway, a prospective registry of TaTME showed higher anastomotic leak rates as well as higher local recurrence rates compared with standard laparoscopic TME (Wasmuth et al. 2020), leading to a moratorium on the procedure (Larsen et al. 2019). COLOR III is an international, multi-center, superiority RCT which has been designed to compare TaTME with laparoscopic TME, and will hopefully provide surgeons with more confidence in deciding between both approaches (Deijen et al. 2016).

Complete Mesocolic Excision (CME)

Success with the TME technique in dramatically improving oncologic outcomes has led to the consideration of a similar surgical approach in cancers of the right colon. Hohenberger described a similar technique in the right colon, using sharp dissection to remove the visceral peritoneum off the retroperitoneum, combined with central vascular ligation to maximize the lymph node harvest (Hohenberger et al. 2009). The main advantage of this technique is in the increased lymph node harvest, particularly lymph nodes situated close to the root of the vasculature, which have been associated with worse outcomes. In a study by Zenger et al., three-year overall survival and disease-free survival were significantly worse amongst stage III patients with metastases to the central vascular lymph nodes (Zenger et al. 2021). Thus far, there has only been one randomized controlled trial which has compared conventional right hemicolectomy with CME right hemicolectomy (Di Buono et al. 2021). This study showed that CME right hemicolectomy was associated with a greater lymph node harvest with no increase in surgical or postoperative complications. While longer-term oncologic outcomes have yet to be published, meta-analyses of retrospective studies have indicated improved oncologic outcomes amongst patients who have undergone CME right hemicolectomy [49–51]. In one meta-analysis, three-year overall survival and five-year disease-free survival were both found to be significantly improved in patients who had undergone CME right hemicolectomy (Anania et al. 2021).

Pelvic Exenteration

Pelvic exenteration is surgery performed for locally advanced and recurrent pelvic cancers. These complex surgical procedures often entail multi-visceral resections to achieve clear margins, and commonly involve multiple surgical specialties including colorectal, urology, gynecology, plastic surgery, and orthopedics. This is particularly important as achieving a R0 resection has been found to be the most important factor in predicting overall survival (Koh et al. 2022). Given the complexity of these procedures, pelvic exenteration is often performed only at high-volume centers of excellence, which concentrate expertise to ensure the best outcomes.

Modern Adjuncts to Oncologic Colorectal Surgery

Surgeons are ultimately limited in our ability to visualize anatomy, and modern adjuncts have been developed which have helped surgeons to see better during an operation. This could potentially lead to the recognition of danger before it has occurred, and lead to reduced morbidity and mortality. In this section, cutting-edge technology which is still in the nascent stage will be explored.

Indocyanine Green (ICG)

Indocyanine green is a water-soluble dye which has a short half-life of three to five minutes (Keller et al. 2017). This dye absorbs light at an excitation wavelength of 750 to 800 nm, and emits light at a higher wavelength of 830 nm (Alander et al. 2012). These characteristics make it suitable for use during surgery as a modality to increase the visibility of critical structures. One key area in which ICG may be used is to visualize perfusion to an anastomosis made following a major resection. Given that anastomotic leaks are major sources of morbidity and mortality in colorectal surgery, the use of ICG as an adjunct to assessing perfusion to the anastomosis has been shown in meta-analyses to significantly reduce this risk (Chan et al. 2020). Another major morbidity during surgery is ureteric injury, particularly during repeat surgery in which natural planes have been disrupted. Fluorescent ureterography has been used to aid in the visualization of the ureter during colorectal surgery (Satish et al. 2022). Finally, ICG has also been applied to the identification of lymph nodes outside the usual resection plane, such as at the inguinal region or lateral pelvic side wall. Such surgery is usually performed laparoscopically, precluding the use of tactile sensation to identify lymph nodes. As it can often be challenging to pick out a single enlarged lymph node, ICG can help in the visual identification of enlarged lymph nodes as they would tend to concentrate ICG relative to its surroundings (Sun et al. 2022; Zhou et al. 2019).

HoloLens

HoloLens (Microsoft Corporation, Redmond, WA) is a head-mounted display which provides 3-dimensional (ED) visualization of the surgical field. This technology provides the surgeon with a mixed reality, given that a 3D image is superimposed onto the surgical field. This 3D image can take the form of the patient's vasculature, and could potentially help guide the harvesting of lymph nodes which might have been seen on computed tomography imaging. This technology has thus far been described in the resection of colorectal liver metastases (Saito et al. 2020). Users of this technology have described the key advantages being no reliance on a sterilized display monitor, improved spatial awareness of key anatomic structures, as well as shared image among all surgeons of the surgical field. This technology will need to be validated and explored in a spectrum of other surgical applications, but has the potential to revolutionize how surgical teams function together, and how surgery is performed.

3D Printing

Another novel technology which has been used to augment the surgeon's appreciation of anatomy is the use of 3D printing technology. Already, current CT scanning machines are able to perform 3D reconstruction of images. Using 3D printing technology, a physical render of the reconstruction can be constructed. There have been a number of authors who have described the application of this technology during surgery, with the bulk of applications being for use in the pre-operative planning phase. Some specific examples of its use include 3D models of the pelvis for use in low rectal cancer, reconstruction of the pelvic side wall to facilitate lateral pelvic lymph node dissection, and to delineate the anatomy in the setting of recurrent disease at the infrarenal region (Przedlacka et al. 2021). 3D models have also been useful to teach surgical trainees and medical students about pelvic anatomy (Hassinger et al. 2010).

Areas for Further Research

The next frontier of colorectal cancer research will involve bringing the proverbial bench and bedside together. Colorectal surgeons today continue to rely on predominantly clinical parameters to stage cancer, or to prepare a patient for surgery. There is however increasing evidence that colorectal cancer can and should be subtyped beyond the four broad stages. For example, the recent efficacy of dostarlimab, an anti-PD-1 monoclonal antibody, in achieving complete response of mismatch repair deficient, locally advanced rectal cancer, suggests that patients who have been molecularly subtyped can get tailored treatment (Cercek et al. 2022). In this study, inclusion criteria for the trial rested on molecular subtyping, and not on the stage of disease. Our ability to go beyond clinical parameters and to characterize a patient's cancer based on the molecular signatures will herald an era of truly personalized medicine. This will not only require the identification of new molecular markers, but will also require increased scalability of current technologies to meet the needs of the global patient community, while addressing important factors such as bioethical ramifications which may arise based on the technology involved.

Conclusion

This chapter has highlighted the breadth and depth of surgical approaches which are available to treat colorectal cancer. We have structured this chapter by highlighting two opposing trends of minimally invasive and maximally invasive approaches, which although diametrically distinct in surgical philosophy, are similarly undergirded by the principles of clear surgical margins and adequate lymphadenectomy. The future of colorectal surgery must continue to evolve by tapping into other broader surgical and technological trends, with the ultimate aim of improving short-term surgical and long-term oncologic outcomes for patients.

Trusted Websites for Further Reading

https://www.cancer.gov/types/colorectal/hp/colon-treatment-pdq

https://www.cancer.gov/types/colorectal/hp/rectal-treatment-pdq

https://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq

https://www.acpgbi.org.uk/resources/354/guidelines_for_the_management_of_cancer_of_the_colon_rectum_and_anus_2017

https://fascrs.org/ascrs/media/files/downloads/2022-colon-cancer-cpg.pdf

https://fascrs.org/ascrs/media/files/downloads/rectal-cancer-cpg-2020.pdf

https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1428

https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1461

References

Adam, I.J., Mohamdee, M.O., Martin, I.G. et al. (1994). Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 344 (8924): 707–711.

Alander, J.T., Kaartinen, I., Laakso, A. et al. (2012). A review of indocyanine green fluorescent imaging in surgery. *Int J Biomed Imaging* 2012: 940585.

Allaix, M.E., Arezzo, A., and Morino, M. (2016). Transanal endoscopic microsurgery for rectal cancer: T1 and beyond? An evidence-based review. *Surg Endosc* 30 (11): 4841–4852.

Amin, M., Edge, S., and Greene, F. (2017). *Et alAJCC Cancer Staging Manual*. New York: Springer.

Anania, G., Davies, R.J., Bagolini, F. et al. (2021). Right hemicolectomy with complete mesocolic excision is safe, leads to an increased lymph node yield and to increased survival: results of a systematic review and meta-analysis. *Tech Coloproctol* 25 (10): 1099–1113.

Baek, S.K., Carmichael, J.C., and Pigazzi, A. (2013). Robotic surgery: colon and rectum. *Cancer J* 19 (2): 140–146.

Bonjer, H.J., Deijen, C.L., Abis, G.A. et al. (2015). A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 372 (14): 1324–1332.

Cercek, A., Lumish, M., Sinopoli, J. et al. (2022). PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med* 386: 2363–2376.

Chan, D.K.H. and Buczacki, S.J.A. (2022). Stage migration - a negative quality indicator in colon cancer management. *Colorectal Dis* 24 (2): 153–154.

Chan, D.K.H., Lee, S.K.F., and Ang, J.J. (2020). Indocyanine green fluorescence angiography decreases the risk of colorectal anastomotic leakage: systematic review and meta-analysis. *Surgery* 168 (6): 1128–1137.

Chang, H.C., Huang, S.C., Chen, J.S. et al. (2012). Risk factors for lymph node metastasis in pT1 and pT2 rectal cancer: a single-institute experience in 943 patients and literature review. *Ann Surg Oncol* 19 (8): 2477–2484.

Clinical Outcomes of Surgical Therapy Study Group; Nelson, H., Sargent, D.J. et al. (2004). A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 350 (20): 2050–2059.

De Simoni, O., Barina, A., Sommariva, A. et al. (2021). Complete mesocolic excision versus conventional hemicolectomy in patients with right colon cancer: a systematic review and meta-analysis. *Int J Colorectal Dis* 36 (5): 881–892.

Deijen, C.L., Velthuis, S., Tsai, A. et al. (2016). COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer. *Surg Endosc* 30 (8): 3210–3215.

Detering, R., Roodbeen, S.X., van Oostendorp, S.E. et al. (2019). Three-year nationwide experience with transanal total mesorectal excision for rectal cancer in the Netherlands: a propensity score-matched comparison with conventional laparoscopic total mesorectal excision. *J Am Coll Surg* 228 (3): 235–244.e1.

Di Buono, G., Buscemi, S., Cocorullo, G. et al. (2021). Feasibility and safety of laparoscopic complete mesocolic excision (CME) for right-sided colon cancer: short-term outcomes. A randomized clinical study. *Ann Surg* 274 (1): 57–62.

Dillman, R.O., Aaron, K., Heinemann, F.S., and McClure, S.E. (2009). Identification of 12 or more lymph nodes in resected colon cancer specimens as an indicator of quality performance. *Cancer* 115 (9): 1840–1848.

Ferri, V., Vicente, E., Quijano, Y. et al. (2021). Right-side colectomy with complete mesocolic excision vs conventional right-side colectomy in the treatment of colon cancer: a systematic review and meta-analysis. *Int J Colorectal Dis* 36 (9): 1885–1904.

Fleshman, J., Branda, M.E., Sargent, D.J. et al. (2019). Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Ann Surg* 269 (4): 589–595.

Green, B.L., Marshall, H.C., Collinson, F. et al. (2013). Long-term follow-up of the medical research council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. *Br J Surg* 100 (1): 75–82.

Guillou, P.J., Quirke, P., Thorpe, H. et al. (2005). Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 365 (9472): 1718–1726.

Hashiguchi, Y., Hase, K., Ueno, H. et al. (2011). Optimal margins and lymphadenectomy in colonic cancer surgery. *Br J Surg* 98 (8): 1171–1178.

Hassinger, J.P., Dozois, E.J., Holubar, S.D. et al. (2010). Virtual pelvic anatomy simulator: a pilot study of usability and perceived effectiveness. *J Surg Res* 161 (1): 23–27.

Heald, R.J. (1988). The 'Holy Plane' of rectal surgery. *J R Soc Med* 81 (9): 503–508.

Heintz, A., Mörschel, M., and Junginger, T. (1998). Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. *Surg Endosc* 12 (9): 1145–1148.

Hohenberger, W., Weber, K., Matzel, K. et al. (2009). Standardized surgery for colonic cancer: complete mesocolic excision and central ligation–technical notes and outcome. *Colorectal Dis* 11 (4): 354–364; discussion 364–365.

Jayne, D., Pigazzi, A., Marshall, H. et al. (2017). Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. *Jama* 318 (16): 1569–1580.

Keller, D.S., Ishizawa, T., Cohen, R., and Chand, M. (2017). Indocyanine green fluorescence imaging in colorectal surgery: overview, applications, and future directions. *Lancet Gastroenterol Hepatol* 2 (10): 757–766.

Kim, M.J., Park, S.C., Park, J.W. et al. (2018). Robot-assisted versus laparoscopic surgery for rectal cancer: a phase II open label prospective randomized controlled trial. *Ann Surg* 267 (2): 243–251.

Koh, C.E., Brown, K.G.M., Steffens, D. et al. (2022). What constitutes a clear margin in patients with locally recurrent rectal cancer undergoing pelvic exenteration? *Ann Surg* 275 (1): 157–165.

Lacy, A.M., García-Valdecasas, J.C., Delgado, S. et al. (2002). Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 359 (9325): 2224–2229.

Lal, N., Chan, D.K.H., Ng, M.E. et al. (2022). Primary tumour immune response and lymph node yields in colon cancer. *Br J Cancer* 126 (8): 1178–1185.

Larsen, S.G., Pfeffer, F., and Kørner, H. (2019). Norwegian moratorium on transanal total mesorectal excision. *Br J Surg* 106 (9): 1120–1121.

Lee, W., Lee, D., Choi, S., and Chun, H. (2003). Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer. *Surg Endosc* 17 (8): 1283–1287.

Manceau, G., Alves, A., Meillat, H. et al. (2022). What is the optimal elective colectomy for splenic flexure cancer: end of the debate? A multicenter study from the GRECCAR group with a propensity score analysis. *Dis Colon Rectum* 65 (1): 55–65.

McDonald, J.R., Renehan, A.G., O'Dwyer, S.T., and Haboubi, N.Y. (2012). Lymph node harvest in colon and rectal cancer: current considerations. *World J Gastrointest Surg* 4 (1): 9–19.

Munini, M., Popeskou, S.G., Galetti, K et al. (2021). Transanal (TaTME) vs. laparoscopic total mesorectal excision for mid and low rectal cancer: a propensity score-matched analysis of early and long-term outcomes. *Int J Colorectal Dis* 36 (10): 2271–2279.

Nagtegaal, I.D., van de Velde, C.J., van der Worp, E. et al. (2002). Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 20 (7): 1729–1734.

Ng, S.S., Leung, K.L., Lee J.F. et al. (2009). Long-term morbidity and oncologic outcomes of laparoscopic-assisted anterior resection for upper rectal cancer: ten-year results of a prospective, randomized trial. *Dis Colon Rectum* 52 (4): 558–566.

Ng, S.S., Lee, J.F., Yiu, R.Y. et al. (2014). Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomized trial. *Surg Endosc* 28 (1): 297–306.

Ourô, S., Ferreira, M., Roquete, P., and Maio, R. et al. (2022). Transanal versus laparoscopic total mesorectal excision: a comparative study of long-term oncological outcomes. *Tech Coloproctol* 26 (4): 279–290.

Pang, A.J., Marinescu, D., Morin, N. et al. (2022). Segmental resection of splenic flexure colon cancers provides an adequate lymph node harvest and is a safe operative approach - an analysis of the ACS-NSQIP database. *Surg Endosc* 36.

Park, J.W., Kang, S.B., Hao, J. et al. (2021). *Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): 10-year follow-up of an open-label, non-inferiority, randomised controlled trial*. *Lancet Gastroenterol Hepatol* 6 (7): 569–577.

Przedlacka, A., Pellino, G., Fletcher, J. et al. (2021). Current and future role of three-dimensional modelling technology in rectal cancer surgery: a systematic review. *World J Gastrointest Surg* 13 (12): 1754–1769.

Rørvig, S., Schlesinger, N., Mårtensson, N.L. et al. (2014). Is the longitudinal margin of carcinoma-bearing colon resections a neglected parameter? *Clin Colorectal Cancer* 13 (1): 68–72.

Saito, Y., Sugimoto, M., Imura, S. et al. (2020). Intraoperative 3D hologram support with mixed reality techniques in liver surgery. *Ann Surg* 271 (1): e4–e7.

Satish, V.N.V.R., Acharya, A., Ramachandran, S. et al. (2022). Fluorescent ureterography with indocyanine green in laparoscopic colorectal surgery: a safe method to prevent intraoperative ureteric injury. *J Minim Access Surg* 18 (2): 320–323.

Schellenberg, A.E., Moravan, V., and Christian, F. (2022). A competing risk analysis of colorectal cancer recurrence after curative surgery. *BMC Gastroenterol* 22 (1): 95.

Scott, K.W. and Grace, R.H. (1989). Detection of lymph node metastases in colorectal carcinoma before and after fat clearance. *Br J Surg* 76 (11): 1165–1167.

Shen, S.S., Haupt, B.X., Ro, J.Y. et al. (2009). Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. *Arch Pathol Lab Med* 133 (5): 781–786.

Smith, H.G., Skovgaards, D.M., Chiranth, D., and Schlesinger, N.H. (2022). The impact of subdivisions of microscopically positive (R1) margins on patterns of relapse in stage III colorectal cancer - A retrospective cohort study. *Colorectal Dis* 24.

Song, S.H., Park, J.S., Choi, G.S. et al. (2021). Impact of the distal resection margin on local recurrence after neoadjuvant chemoradiation and rectal excision for locally advanced rectal cancer. *Sci Rep* 11 (1): 22943.

Stevenson, A.R.L., Solomon, M.J., Brown, C.S.B. et al. (2019). Disease-free survival and local recurrence after laparoscopic-assisted resection or open resection for rectal cancer: the Australasian laparoscopic cancer of the rectum randomized clinical trial. *Ann Surg* 269 (4): 596–602.

Sun, Y., Lin, Y, Liu, Z. et al. (2022). Combined laparoscopic lymphoadenectomy of lateral pelvic and inguinal nodal metastases using indocyanine green fluorescence imaging guidance in low rectal cancer after preoperative chemoradiotherapy: a case report. *BMC Gastroenterol* 22 (1): 123.

van der Pas, M.H., Haglind, E., Cuesta, M.A. et al. (2013). Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 14 (3): 210–218.

van Oostendorp, S.E., Belgers, H.J., Bootsma, B.T. et al. (2020). Locoregional recurrences after transanal total mesorectal excision of rectal cancer during implementation. *Br J Surg* 107 (9): 1211–1220.

Vogel, J.D., Felder, S.I., Bhama, A.R. et al. (2022). The American society of colon and rectal surgeons clinical practice guidelines for the management of colon cancer. *Dis Colon Rectum* 65 (2): 148–177.

Wasmuth, H.H., Faerden, A.E., Myklebust, T.Å. et al. (2020). Transanal total mesorectal excision for rectal cancer has been suspended in Norway. *Br J Surg* 107 (1): 121–130.

Wibe, A., Rendedal, P.R., Svensson, E. et al. (2002). Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 89 (3): 327–334.

Yan, H., Wang, P.Y., Wu, Y.C., and Liu, Y.C. (2022). Is a distal resection margin of ≤ 1 cm safe in patients with intermediate- to low-lying rectal cancer? A systematic review and meta-analysis. *J Gastrointest Surg* 26.

Zenger, S., Aytac, E., Gurbuz, B. et al. (2021). Metastasis to lymph nodes around the vascular tie worsens long-term oncological outcomes following complete mesocolic excision and conventional colectomy for right-sided colon cancer. *Tech Coloproctol* 25 (3): 309–317.

Zhou, S.C., Tian, Y.T., Wang, X.W. et al. (2019). Application of indocyanine green-enhanced near-infrared fluorescence-guided imaging in laparoscopic lateral pelvic lymph node dissection for middle-low rectal cancer. *World J Gastroenterol* 25 (31): 4502–4511.

Stoma

Theophilus Anyomih, Mudassar Majeed & Justin Davies

Definition

The term “ostomy” comes from the Greek “stoma” and means “mouth.” In medical terms, a stoma/ostomy refers to a communication, natural or artificial, temporary or permanent between a body cavity and the external environment. An enterostomy is a surgically fashioned intestinal opening or diversion of bowel continuity of which ileostomy or colostomy are the most common.

Brief History

Surgical formation of intestinal stomas was rare in the pre-anesthetic era. The earliest report of formation of surgical stoma was by Littre – he created a stoma in a diseased child with imperforate anus (Littre 1732). It was not until 1793 when the first successful colostomy on a three-year-old with imperforate anus was undertaken – the patient lived up to the age of 45 years (Cataldo 1999; Duret 1798).

The advent of anesthetic techniques made intestinal stoma formation safer, practical and more common. An ileostomy was first advocated in ulcerative colitis in the early 1900s but became widely accepted after Dr Bryan Brooke made surgical maturation the standard of care for ileostomy. Shortly thereafter, surgical maturation became the standard of care for colostomy construction as well (Cataldo 1999; Hardy 1989; Weakley 1994).

Types/Classification of Intestinal Stoma

Stomas can be classified based on the anatomical parts of the involved structure; ileostomy, colostomy, jejunostomy or less commonly caecostomy, and appendicostomy. A urostomy (or ileal conduit) is quite commonly fashioned to serve as a conduit for urinary diversion after cystectomy.

A stoma can also be classified as either a loop or an end stoma. A loop stoma is formed by externalizing a loop of bowel and creating a proximal and distal opening. Intestinal content empties via the proximal/afferent opening. The distal loop is adjacent to the proximal loop and makes for a technically more simple closure by mobilizing the two ends, anastomosing them, and placing the joined bowel back in the abdominal cavity through the same opening. A loop stoma is mainly indicated to protect a distal anastomosis, thereby reducing the risk of anastomotic leak. Some studies have demonstrated fewer complications with loop defunctioning ileostomy compared to a loop colostomy (Saunders and Hemingway 2008; Williams et al. 1986).

An end stoma is formed from the proximal end of the divided bowel. The usual location of a sigmoid end colostomy is the left iliac fossa – as performed during a Hartmann’s procedure (classically described as a sigmoid resection, end colostomy, and remaining closed rectal stump). Sometimes a mucus fistula may be created in addition to an end colostomy by bringing out the distal end of the divided colon, either through the same opening as the colostomy (forming a double-barrel stoma) or through a separate incision. Mucus fistulas are created if there is high risk that the distal stump closure might break down.

An end ileostomy is usually sited in the right iliac fossa and is commonly fashioned from the most distal viable ileum. Reversal of end stomas can be via a minimally invasive or open approach.

Based on functional purposes a stoma can be temporary or permanent. Temporary diverting stomas are usually created to protect a distal anastomosis, to relieve an obstruction or to rest the distal bowel. Permanent stomas are typically indicated when a primary anastomosis is not possible (e.g. very low rectal cancer involving the sphincter complex requiring an abdominoperineal excision of the rectum – APER), not safe (e.g. in a patient with significant comorbidity who would not be able to tolerate potential septic complications from an anastomotic leak) or not appropriate (e.g. a patient with pre-existing poor bowel function/continence).

Indications

There are several indications for the different types of stomas. End ileostomies are indicated after panproctocolectomy (single procedure or staged, according to indication) for hereditary bowel cancer – FAP/HNPCC (especially when in association with low rectal cancer), ulcerative colitis refractory to medical therapy or refractory Crohn’s colitis.

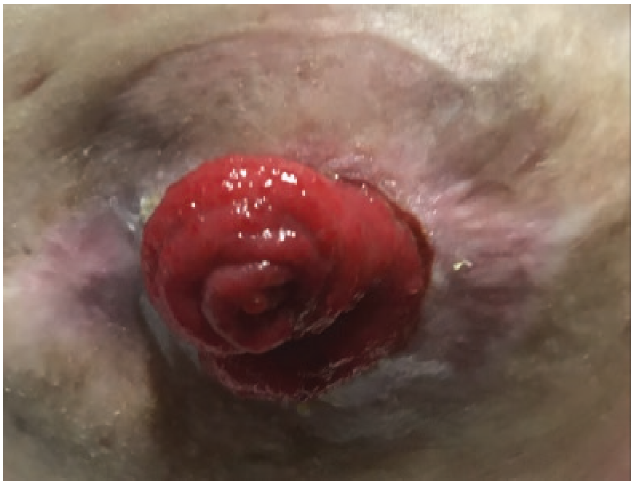

Figure 1 Loop ileostomy.

Defunctioning loop ileostomy is typically formed to protect a distal rectal anastomosis (e.g. low anterior resection), relieve a distal obstruction (e.g. malignant/inflammatory stricture) or to defunction an intestinal fistula. It can be fashioned to prevent contamination and allow healing of anorectal trauma or anal sphincter injury. In the presence of severe perianal sepsis (e.g. Crohn's disease), a defunctioning loop stoma to prevent worsening of sepsis and relieve symptoms is particularly useful (see Figure 1).

An end colostomy is used in a Hartmann's procedure, after a low rectal cancer resection or anal cancer salvage surgery where sphincter complex excision is necessary (APER) or in rectal cancer surgery where a low colorectal or coloanal anastomosis is deemed inappropriate, often to avoid the risks of potential anastomotic leak or if the functional sequelae of a low anastomosis are not acceptable. It can also be useful in cases of intractable faecal incontinence.

Defunctioning loop colostomy may be indicated in relieving distal obstruction (e.g. malignant/inflammatory stricture causing a distal large bowel obstruction), defunctioning complex perianal fistulas, and in the setting of Fournier's gangrene in conjunction with extensive perineal debridement. Some patients with locally advanced and symptomatic rectal cancer may require a defunctioning loop stoma prior to commencing neoadjuvant chemoradiotherapy. Finally, in inoperable rectal carcinoma, it can be performed as a palliative procedure, although palliative radiotherapy may offer more appropriate symptom relief.

Stoma Siting

Patients who undergo stoma surgery face multiple challenges and lifestyle changes (WOCN Society Clinical Guideline: Management of the Adult Patient With a Fecal or Urinary Ostomy-An Executive Summary 2018). Appropriate siting of a stoma is critical as an error can result in significant impact in the patients' quality of life after surgery. Correct stoma siting/marking and meticulous construction of the stoma are factors that reduce complications from stomas and peristomal skin complications and are important in allowing for stoma self-care, independence and resumption of normal activities (Hendren et al. 2015). Whenever possible, the stoma site should be selected and marked by a specialist stoma nurse. They should be involved early on as among other things, they discuss the principles and practicalities of living with a stoma and counsel the patient in advance of surgery. Sometimes, the patient may choose to discuss lifestyle issues with other ostomates to help with shared decision making, and the specialist stoma nurse is often able to facilitate this.

The stoma site should be on a flat, smooth area of the skin devoid of scars, skin creases and bony prominences. The selected area should be visible to the patient and accessible so they can manage it appropriately after surgery. When planning for a stoma site, the patient should ideally be dressed in their normal clothes and should be assessed standing, sitting and lying down.

Another factor to consider when choosing a site for stoma formation is when surgery involves multiple sites; fecal and urinary stomas (e.g. after a pelvic exenteration) should be sited at different horizontal levels, and generally on opposite sides of the abdomen.

Complications of Stoma Formation

A poorly constructed stoma can impact a patient's outcome, and result in difficult management issues. Moreover, complications such as hernia, prolapse, retraction, and stenosis can occur despite the best circumstances. It is important to understand how to avoid and manage these issues (Strong Scott 2016).

Early Complications

Ischemia/necrosis

This is more common following colostomy formation than ileostomy. Incidence ranges from 1.6–11% (Cross et al. 2017; Franklyn et al. 2017; Whiteley et al. 2016; Zindel et al. 2017). Signs of ischemia usually arise within 24 hours of surgery, although delayed ischemia can also occur due to underlying medical conditions causing hypoperfusion. The causes of ischemia/necrosis are mainly associated with surgical technique in creation of the stoma and include tension on the mesentery or ligation of the primary blood vessel/damage to blood supply of the distal end of the stoma. The latter is typically due to extensive mesenteric dissection or skeletonization of the distal bowel. A large abdominal pannus in obese patients and a tight abdominal wall opening through which the stoma passes can also precipitate ischemia. It is essential in the early postoperative period to perform daily assessment of any formed stoma looking for ischemia. It can be difficult to differentiate between necrosis and hematoma.

Revision of a necrotic stoma depends on the level of necrosis in the abdominal wall. A stoma that is necrotic proximal to the fascial opening requires revisional surgery. Early, less critical, and more distal stoma ischemia can lead to stenosis as a later complication.

Fluid and Electrolyte Imbalances

These imbalances are more common in patients with an ileostomy. A newly formed ileostomy usually functions within 24 hours, producing an average of 1200 ml of stool daily. Subsequent ileostomy adaptation (body's compensatory response to prevent dehydration by increasing mean plasma aldosterone) maintains ileostomy output to about 300–700 ml daily. Despite this compensatory mechanism, dehydration from high output stomas (>1000 ml daily) occurs in 16% of ostomates (Arenas Villafranca et al. 2015; Baker et al. 2011). Several factors contribute to this, including incomplete bowel obstruction, intra-abdominal sepsis, prokinetic drugs, sudden withdrawal of steroids or opiates, enteritis with Clostridium difficile infection, diuretics, coexisting diabetes mellitus and total proctocolectomy.

Intravenous fluid and electrolyte resuscitation, oral fluid intake restriction, avoiding hypotonic drinks and triggering drugs are recommended management strategies. Also, close monitoring of body weight, fluid balance, serum biochemistry, and electrolytes is mandatory in the immediate postoperative period.

Mucocutaneous Separation

Mucocutaneous separation (MCS) is characterized by partial or circumferential detachment of the mucosa from the peristomal skin. The disruption can trigger wound breakdown and appliance leakage in the early postoperative period. A combination of factors that can lead to MCS include infection, diabetes mellitus, corticosteroids, malnutrition, excessive tension on the stoma, and stoma necrosis (Kim and Kumar 2006; Steinhagen et al. 2017). The incidence of MCS is 3.7–9.7% (Franklyn et al. 2017; Miyo et al. 2017; Sung et al. 2010).

It is generally treated conservatively with local wound care and fastidious pouching technique. The separated area is irrigated with saline, and skin barrier powder is used to absorb exudates and fill the defect before applying the pouching system. If the separation is deep, it may be effective to fill the separation using alginate or gelling fiber and cover it with a solid hydrocolloid or the pouch's skin barrier (WOCN Society Clinical Guideline: Management of the Adult Patient With a Fecal or Urinary Ostomy-An Executive Summary 2018). Circumferential MCS is treated in a similar fashion but may predispose to eventual retraction and stenosis.

Retraction

Retraction is the inversion of the mucocutaneous junction toward the abdominal wall musculature and is often the consequence of insufficient length of intestine or inadequate mobilization at the time of operation, especially in obese patients (see Figure 2). It can also be a sequelae of stoma ischemia and necrosis. The incidence is 2.9–5.4% (Güenaga et al. 2007; Miyo et al. 2017; Mohan et al. 2019). Traditionally, stoma rods have been used to prevent retraction in loop stomas, although a meta analysis showed that its use for loop stomas did not prevent retraction but was associated with higher incidence of peristomal dermatitis and stoma necrosis (Mohan et al. 2019). The definitive management is stoma revision with adequate bowel length and blood supply.

Other early complications of stoma formation include bleeding, hematoma formation, edema of the stoma and cutaneous irritation, sometimes with ulceration. "Twisting" of the stoma will present in the early postoperative period as bowel obstruction. The "twist" may be because of failure to orient the stoma appropriately at the time of surgery or could be related to a volvulus of, for example, small bowel around the ileostomy.

Late Complications

Parastomal Hernia (PSH)

This is an incisional hernia at the stoma site. The reported incidence ranges from 3–50% and increases over time. The risk factors for PSH can be patient related or due to surgical technical factors (Krishnamurty et al. 2017; Osborne et al. 2018).

Patient factors include obesity, malnutrition, advanced age, smoking, collagen abnormalities, corticosteroid use and any

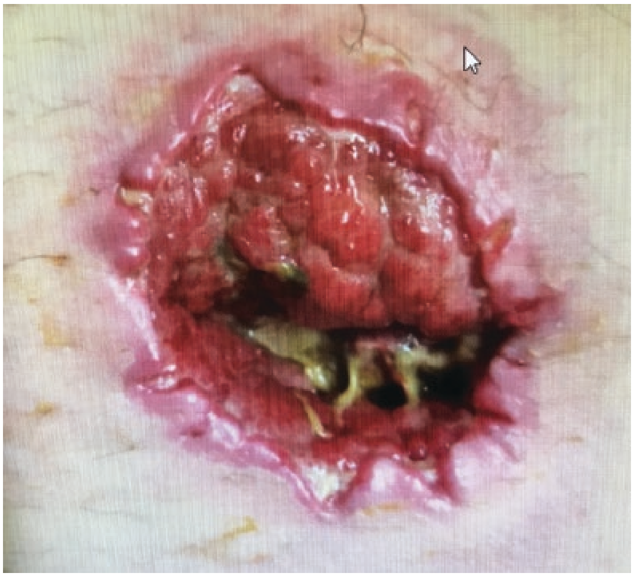

Figure 2 Stoma Retraction.

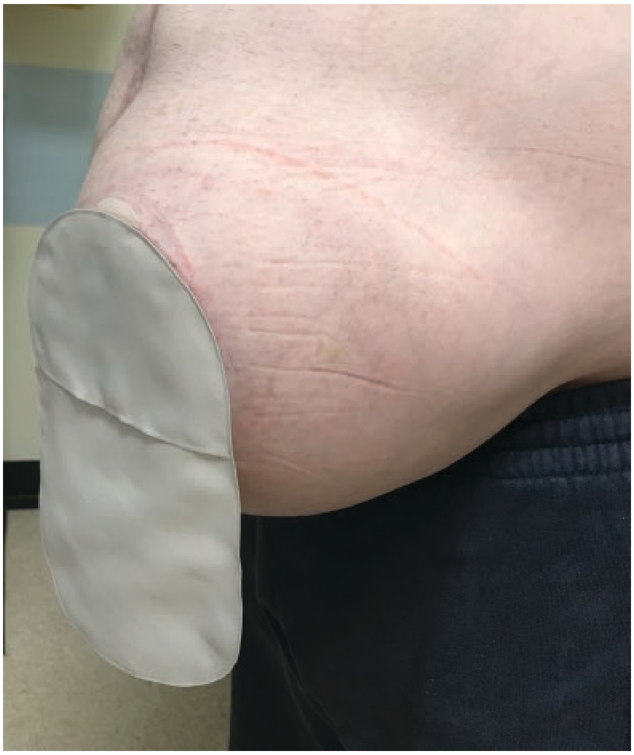

Figure 3 Parastomal Hernia.

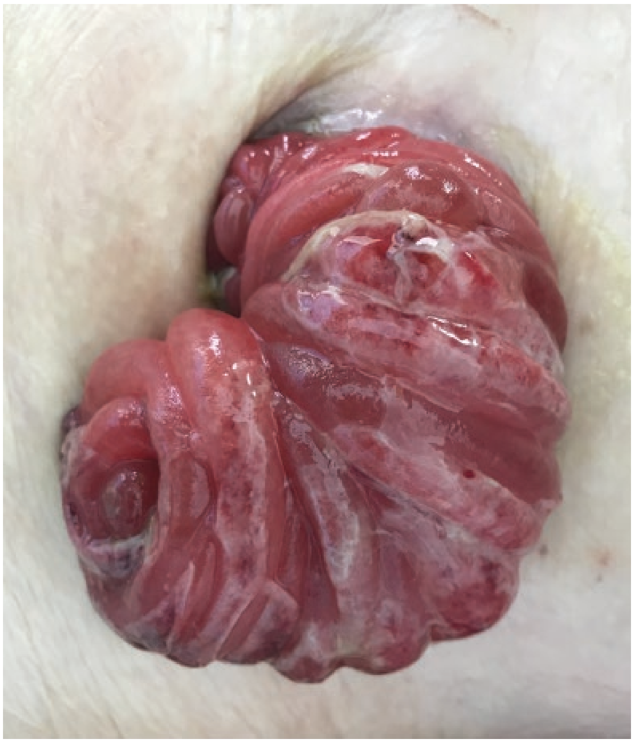

Figure 4 Stoma Prolapse.

condition that increases intra-abdominal pressure. Surgical or technical factors that increase the risk of PSH formation are inappropriate stoma site selection, oversized fascial trephine size, excessive splitting and stretching of the abdominal rectus muscle and emergency stoma creation (see Figure 3).

The risk of PSH can be reduced with management of body weight, exercise, and surgically by extraperitoneal rather than transperitoneal stoma construction (Kroese et al. 2016). The use of prophylactic mesh placement during the initial stoma creation may be preventive (Cross et al. 2017; Jones et al. 2018).

Management of PSH can be conservative with hernia support belts and a flexible pouching system, with discontinuation of any stoma irrigation (WOCN Society Clinical Guideline: Management of the Adult Patient With a Fecal or Urinary Ostomy-An Executive Summary 2018). Surgical management could be in the elective setting after risk-benefit analysis. Repair is indicated as an emergency when the PSH is complicated by incarceration or a non-resolving bowel obstruction. Mesh repair is the standard treatment, (ACPGBI Parastomal Hernia Group 2018; Hansson et al. 2012) although the optimal technique and site of mesh placement remains elusive.

Stoma Prolapse

This is a full-thickness protrusion of the bowel through the stoma site and may occur because of an excessive length of redundant intra-abdominal bowel or a large fascial opening (see Figure 4). It is more commonly seen in transverse loop colostomy with incidence as high as 30% (Husain and Cataldo 2008; Shabbir and Britton 2010). The incidence rate is 2–3% in ileostomies and 2–10% in end colostomies (Correa-Marinez et al. 2018; Krishnamurty et al. 2017; Miyo et al. 2017). There is often a co-existing PSH.

The risk factors associated with this are advanced age, obesity, increased intra-abdominal pressure, chronic obstructive pulmonary disease, bowel redundancy, and weak fascia (Kim and Kumar 2006; Krishnamurty et al. 2017). Technical factors associated with stoma prolapse include improper stoma site (outside the rectal muscle), oversized fascial aperture and redundancy of the bowel at the stoma site (Kim and Kumar 2006; Maeda et al. 2003). Definitive management is surgical revision of the stoma or where indicated, restoration of intestinal continuity. This can be done in the elective setting if the prolapse is reducible and not concerning for ischemia. Otherwise, urgent surgical management is required.

Parastomal Varices

This is most common in patients with primary sclerosing cholangitis (PSC) and liver cirrhosis. It leads to recurrent bleeding in about 5% of all ostomates (Pennick and Artioukh 2013; Setaihi et al. 2016). Portal hypertension causes enlarged and dilated venous channels to develop at the junction between the high-pressure portal and the low-pressure venous systems. The collateral porto-systemic anastomosis forms at the mucocutaneous junction resulting in engorged subcutaneous vessels (Krishnamurty et al. 2017; Pennick and Artioukh 2013).

Direct pressure with adrenaline-soaked gauze should be initially attempted in cases of acute bleeding. Suture ligation and/or electrocauterization may be needed for refractory bleeding. A transjugular intrahepatic portosystemic shunt (TIPSS) procedure should be considered in order to reduce the portal pressure. As a final resort, surgical portosystemic shunt procedures with mesocaval, portocaval, or splenorenal anastomosis can achieve reduced re-bleeding rates (38%) compared to the local management techniques, but are associated with increased morbidity and mortality (Pennick and Artioukh 2013), being rarely performed nowadays

Peristomal Skin Conditions

These occur in up to 40% of patients with an ileostomy and 7–20% of those with a colostomy (Salvadalena 2008). Issues include leakage/chemical irritation, pyoderma gangrenosum, suture sinus/granulation tissue and allergic contact dermatitis. Leakage/chemical irritation are more common in those with an ileostomy due to the continuous production of watery, alkaline, effluent rich in proteolytic enzymes that irritate exposed peristomal skin. If this persists, it results in loss of skin integrity and maceration and can quickly progress to painful peristomal ulceration.

Pyoderma gangrenosum is a neutrophilic dermatosis associated with progressive skin ulceration, necrosis, and abscess. Sometimes, an immunological response to retained suture material can lead to red, moist lesions at the mucocutaneous junction representing a suture sinus or granulation tissue. Absorbable sutures are most commonly used now for stoma formation, thus making this issue much less common, although significant peristomal granulation tissue can form in response to repeated trauma and poorly fitting stoma appliances.

Patients can suffer allergic contact dermatitis from any ostomy product including the skin barrier, powders, pastes, belts, cleansing products, and adhesives. Formal consultation with a dermatologist/allergist can be helpful.

What Is the Role of Specialist Nursing Care?

The role of the clinical nurse specialist and stoma nurse specialist has many facets, incorporating competencies such as clinical practice, patient pathway coordination, management, consultation, education and research/audit (Marshall and Luffingham 1998). The hospital-based clinical nurse specialist in colorectal cancer can be dual trained in stoma care as well as oncology. Alternatively, the oncology clinical nurse specialist will work closely alongside specialist stoma care nurses to provide a high standard of holistic care to patients with colorectal cancer. Specialist nurse teams can vary depending on the size and location of hospitals and the needs of the local population.

Clinical nurse specialists have a pivotal role in the care of individuals with colorectal cancer and their families, providing information and support from diagnosis, throughout treatment and during follow-up or palliative care. NICE guidance from 2004 states that patients should be able to contact a clinical nurse specialist from the time of their diagnosis and that this should ensure continuity of care and practical help in dealing with the effects of colorectal cancer (National Institute for Health and Clinical Excellence (NICE) 2004). The nurse specialist works as an autonomous practitioner with a caseload of patients, being an expert resource with a sound knowledge base ensuring that the care delivered is research-based and of a high standard. To ensure a smooth pathway through various disciplines the nurse specialist liaises with other members of the MDT, acting as the patient's advocate when treatment decisions are being made. They also communicate frequently with primary care teams, particularly in relation to the urgent two-week wait referral system in the United Kingdom. The recommendation that patients with certain symptoms are investigated promptly and within two weeks of referral from their GP puts the nurse specialist at the center of the patient care pathway, coordinating further referrals to appropriate specialties and informing GPs and patients of relevant diagnoses and plans.

Education and sharing of expertise are paramount in the role of the clinical nurse specialist. The teaching of patients, their families and generalist colleagues on all aspects of stoma care and colorectal cancer is pivotal to providing optimal overall care. In addition, the empowering and motivation of ward nurses, outpatient clinic staff and primary care teams that the nurse specialist can engender allows the building of good working relationships and a more cohesive network of professionals. In order to provide up-to-date care, the clinical nurse specialist should be actively involved in the auditing of services and setting of standards and protocols. It is very important that the results of an audit are incorporated into standard practice, and the clinical nurse specialist can facilitate this by acting as a focus for change and improvements in patient care and pathways

Key Take Home Messages

- Stoma formation is very commonly performed.
- Most common stoma types include loop or end ileostomy or colostomy.
- Stoma complications can occur at any time.
- Specialist nursing care is vital in the management of patients with or being considered for a stoma.

Areas for Further Research

Stoma-related problems have great impact on patient's quality of life.

- Parastomal hernia reduces health-related quality of life and causes limitations in sexual function, travel, social interaction, and return to work. Parastomal hernia prevention and treatment is a very important research topic. The UK-based CIPHER cohort study aims to recruit 4000 patients to investigate the true incidence and prevention of parastomal hernia in patients undergoing elective or expedited surgery (Tabusa et al. 2021).
- Various randomized trials have been performed on the use of prophylactic mesh to prevent parastomal hernia but future research studies should be focusing on the optimal technique to prevent these hernias.

References

ACPGBI Parastomal Hernia Group. (2018 Jul). Prevention and treatment of parastomal hernia: a position statement on behalf of the association of coloproctology of Great Britain and Ireland. *Colorectal Dis* 20 (Suppl 2): 5–19.

Arenas Villafranca, J.J., López-Rodríguez, C., Abilés, J. et al. (2015 May 9). Protocol for the detection and nutritional management of high-output stomas. *Nutr J* 14: 45.

Baker, M.L., Williams, R.N., and Nightingale, J.M. (2011 Feb). Causes and management of a high-output stoma. *Colorectal Dis* 13 (2): 191–197.

Cataldo, P. (1999). Intestinal stomas: 200 years of digging. *Dis Colo Rectum* 42: 137–142.

Correa-Marinez, A., Grenabo, J., Bock, D. et al. (2018 Dec). The type of stoma matters-morbidity in patients with obstructing colorectal cancer. *Int J Colorectal Dis* 33 (12): 1773–1780.

Cross, A.J., Buchwald, P.L., Frizelle, F.A. et al. (2017 Feb). Meta-analysis of prophylactic mesh to prevent parastomal hernia. *Br J Surg* 104 (3): 179–186.

Duret, C. (1798). *Rec Period Soc Med Paris* 4: 45.

Franklyn, J., Varghese, G., Mittal, R. et al. (2017 Jul). A prospective randomized controlled trial comparing early postoperative complications in patients undergoing loop colostomy with and without a stoma rod. *Colorectal Dis* 19 (7): 675–680.

Güenaga, K.F., Lustosa, S.A., Saad, S.S. et al. (2007 Jan24). Review Ileostomy or colostomy for temporary decompression of colorectal anastomosis. *Cochrane Database Syst Rev* (1): CD004647.

Hansson, B.M., Slater, N.J., van der Velden, A.S. et al. (2012 Apr). Surgical techniques for parastomal hernia repair: a systematic review of the literature. *Ann Surg* 255 (4): 685–695.

Hardy, K. (1989). Evolution of the stoma. *Aust N Z J Surg* 59: 71–77.

Hendren, S., Hammond, K., Glasgow, S.C. et al. (2015 Apr). Clinical practice guidelines for ostomy surgery. *Dis Colon Rectum* 58 (4): 375–387.

Husain, S.G. and Cataldo, T.E. (2008 Feb). Late stomal complications. *Clin Colon Rectal Surg* 21 (1): 31–40.

Jones, H.G., Rees, M., Aboumarzouk, O.M. et al. (2018 Jul 20). Review Prosthetic mesh placement for the prevention of parastomal herniation. *Cochrane Database Syst Rev* 7: CD008905.

Kim, J.T. and Kumar, R.R. (2006 Nov). Reoperation for stoma-related complications. *Clin Colon Rectal Surg* 19 (4): 207–212.

Krishnamurty, D.M., Blatnik, J., and Mutch, M. (2017 Jul). Stoma complications. *Clin Colon Rectal Surg* 30 (3): 193–200.

Kroese, L.F., de Smet, G.H., Jeekel, J. et al. (2016 Jul). Systematic review and meta-analysis of extraperitoneal versus transperitoneal colostomy for preventing parastomal hernia. *Dis Colon Rectum* 59 (7): 688–695.

Littre, A. (1732) Diverses observations Anatomiques. II. Histoire de l'Academie Royale des Sciences, Paris, 1710.

Maeda, K., Maruta, M., Utsumi, T. et al. (2003 Jul). Pathophysiology and prevention of loop stomal prolapse in the transverse colon. *Tech Coloproctol* 7 (2): 108–111.

Marshall, Z. and Luffingham, N. (1998). Does the specialist nurse enhance or deskill the general nurse? *Br J Nursing* 7 (11).

Miyo, M., Takemasa, I., Ikeda, M. et al. (2017 Aug). The influence of specific technical maneuvers utilized in the creation of diverting loop-ileostomies on stoma-related morbidity. *Surg Today* 47 (8): 940–950.

Mohan, H.M., Pasquali, A., O'Neill, B. et al. (2019 Mar). Stoma rods in abdominal surgery: a systematic review and metaanalyses. *Tech Coloproctol* 23 (3): 201–206.

National Institute for Health and Clinical Excellence (NICE). (2004). Healthcare services for bowel (colorectal) cancer. Understanding NICE guidance – information for the public. National Institute for Health and Clinical Excellence, London.

Osborne, W., North, J., and Williams, J. (2018 Mar 8). Using a risk assessment tool for parastomal hernia prevention. *Br J Nurs* 27 (5): 15–19.

Pennick, M.O. and Artioukh, D.Y. (2013 Apr). Management of parastomal varices: who re-bleeds and who does not? A systematic review of the literature. *Tech Coloproctol* 17 (2): 163–170.

Salvadalena, G. (2008 Nov-Dec). Incidence of complications of the stoma and peristomal skin among individuals with colostomy, ileostomy, and urostomy: a systematic review. *J Wound Ostomy Continence Nurs* 35 (6): 596–607; quiz 608-9.

Saunders, R.N. and Hemingway, D. (2008). Intestinal stomas. *Surgery* 26: 347–351.

Setaihi, R., Rousset, P., Muller, A. et al. (2016 Apr). Percutaneous treatment of parastomal varices: direct or transhepatic approach? *Diagn Interv Imaging* 97 (4): 491–494.

Shabbir, J. and Britton, D.C. (2010 Oct). Review stoma complications: a literature overview. *Colorectal Dis* 12 (10): 958–964.

Steinhagen, E., Colwell, J., and Cannon, L.M. (2017 Jul). Review intestinal stomas-postoperative stoma care and peristomal skin complications. *Clin Colon Rectal Surg* 30 (3): 184–192.

Strong Scott, A. (2016 Jun). The difficult stoma: challenges and strategies. *Clin Colon Rectal Surg* 29 (2): 152–159. https://doi.org/10.1055/s-0036-1580628.

Sung, Y.H., Kwon, I., Jo, S. et al. (2010 Mar-Apr). Factors affecting ostomy-related complications in Korea. *J Wound Ostomy Continence Nurs* 37 (2): 166–172.

Tabusa, H., Blazeby, J.M., Blencowe, N. et al. (2021). Protocol for the UK cohort study to investigate the prevention of parastomal hernia (the CIPHER study). *Colorectal Dis* 23: 1900–1908.

Weakley, F. (1994). A historical perspective of stomal construction. *J Wound Ostomy Continence Nurs* 21: 59–75.

Whiteley, I., Russell, M., Nassar, N. et al. (2016 Jun). Outcomes of support rod usage in loop stoma formation. *Int J Colorectal Dis* 31 (6): 1189–1195.

Williams, N.S., Nasmyth, D.G., Jones, D., and Smith, A.H. (1986). De-functioning stomas: a prospective controlled trial comparing loop ileostomy with loop transverse colostomy. *Br J Surg* 73: 566–570.

WOCN Society Clinical Guideline: Management of the Adult Patient With a Fecal or Urinary Ostomy-An Executive Summary. (2018 Jan/Feb). Wound, ostomy and continence nurses society., guideline development task force. *J Wound Ostomy Continence Nurs* 45 (1): 50–58.

Zindel, J., Gygax, C., Studer, P. et al. (2017 Jun). A sustaining rod increases necrosis of loop ileostomies: a randomized controlled trial. *Int J Colorectal Dis* 32 (6): 875–881.

Radiotherapy for Colorectal Cancer

Sean M. O'Cathail

Introduction

The management of rectal cancer has undergone a dramatic parallel evolution in multidisciplinary care over the last 40 years (Figure 1). Improvements in preoperative imaging, evolving surgical techniques and new radiotherapy technology have resulted in a significant improvement in reducing local recurrences. Historically in the 1980s local recurrence was as high as 25% when patients were managed with surgery alone (Fisher et al. 1988). By the early 2000s three systematic reviews/meta-analyses examining the role of radiotherapy in resectable rectal cancer conclusively showed that local recurrence was improved with the addition of, predominantly, pre-operative pelvic radiotherapy (Cammà et al. 2000; Colorectal Cancer Collaborative Group 2001; Glimelius et al. 2003). Radiotherapy has been further refined with the addition of radiosensitizing chemotherapy, for example 5-flurouracil, which has further improved responses and decreased local recurrence rates (Bosset et al., 2006; Gérard et al. 2006) but no survival benefit.

In modern practice the expectation is that, with multimodal treatment, local recurrence rates should be ~5%. With this success however interest has shifted to other area of need in rectal management, including how to influence disease metastasis free survival, which has plateaued at 75%, and increasing organ preservation where patients may avoid the need for surgery and the consequent morbidity.

Indications for Pelvic Radiotherapy in an MRI Era

For much of the last 15 years, the use of neoadjuvant pelvic radiotherapy had been a settled issue with short course radiotherapy [SCRT] (25Gy in 5 fractions) or chemoradiotherapy [CRT] (45/50.4Gy in 25/28 fractions) predominating (Glynne-Jones et al. 2017; Benson et al. 2022). High risk features include cT3, threatened or involved mesorectal fascia, low anatomical position, extramural vascular invasion, high nodal burden, or lateral pelvic nodes. As local disease status progresses and high-risk features accumulate, the indications for pelvic radiation increase.

Emergence of Total Neoadjuvant Therapy

Over the last five years, data has accrued to challenge the primacy of CRT in the locally advanced disease (>T3, N+) and advanced disease setting (>T3, MRF involved, lateral node +). The incorporation of systemic treatment, usually 5-FU/Oxaliplatin, into the neoadjuvant window is increasingly employed, with two chief aims: to decrease distant metastasis free survival and to increase local response rates. This strategy has been termed Total Neoadjuvant Therapy (TNT).

Several important Phase III randomized studies (Polish II, STELLAR, RAPIDO) have demonstrated that SCRT and 5FU/oxaliplatin chemotherapy for 6–18 weeks is at least as effective or superior to CRT (Bahadoer et al. 2021; Bujko et al. 2016; Jin et al. 2022) in achieving excellent local control and decreasing distant metastases. Induction chemotherapy, where chemotherapy precedes CRT, initially with FOLFOX (Perez et al.

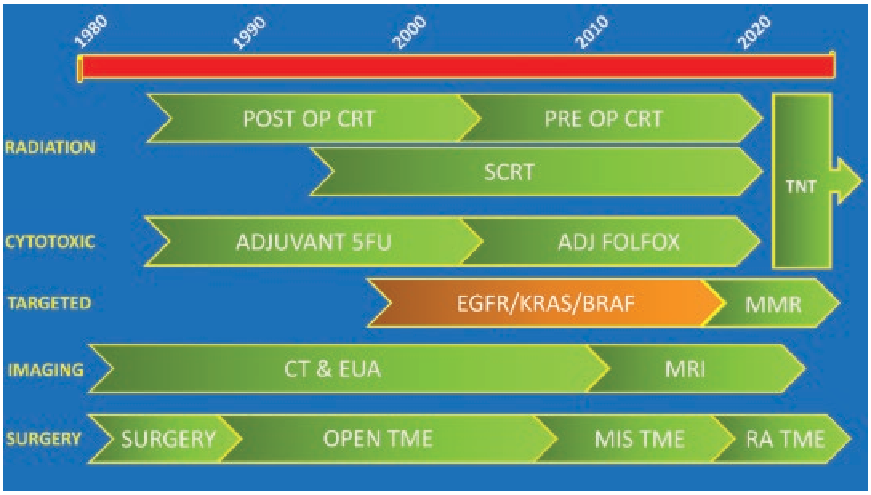

Figure 1 The parallel evolution of the multidisciplinary management of rectal cancer of the last 40+ years; CRT = Chemoradiation; SCRT = Short Course Radiotherapy; 5FU = 5- Fluorouracil; FOLFOX = 5- Fluorouracil, Folinic acid, Oxaliplatin, Leucovorin; TNT = Total Neoadjuvant Therapy; EGFR = Epidermal Growth Factor Receptor: KRAS = Kirsten rat sarcoma virus; BRAF = B-raf Proto-Oncogene serine/threonine Kinase; CT = Computed tomography; EUA = Examination under anesthesia; MRI = Magnetic resonance imaging; TME = Total Mesorectal Excision; MIS = Minimally Invasive Surgery; RA = Robotic Assisted.

2017) and more recently with FOLFIRINOX (Conroy et al. 2021) is also gaining popularity with the latter showing a significant improvement in DFS compared to CRT in a Phase III trial. Taken in aggregate, the incorporation of neoadjuvant systemic treatment in the high-risk disease setting appears to improve survival by decreasing distant relapse, with high treatment compliance rates and no significant increase in surgical morbidity.

One observation from earlier TNT studies was that pathological complete response (pCR) rates were much higher than with CRT, up from ~ 15% to 25–30% (Perez et al. 2017). Subsequent studies have focused on optimizing the response rates by altering the sequencing and duration of chemotherapy within the TNT window. Longer durations of consolidation chemotherapy (after CRT) increased the pCR rate from 25% (2 cycles of FOLFOX) to 38% (6 cycles) in a phase II trial, although some of the effect may have been due to the delay to resection (Garcia-Aguilar et al. 2015). A head-to-head Phase II comparison of induction and consolidation chemotherapy over a 120 day TNT window showed that consolidation increases response rates from 17% to 25% (Fokas et al. 2019). With response rates now at all-time high, and an emerging patient-centered focus on the morbidity of permanent stoma formation, the TNT approach is increasingly used in the pursuit of "organ preservation," where definitive resection is deferred and possible avoided altogether in patients who achieve excellent complete clinical responses. The OPRA trial recently reported total mesorectal excision free survival of 53% at 3 years (Garcia-Aguilar et al. 2022). It should be emphasized however that there is no level 1 evidence in support of the oncological equivalence of organ preservation and TME.

Emerging Biological Differences in Rectal Cancer

Currently there are no biomarkers to help stratify patients to the expanding suite of neoadjuvant strategies. However exciting new data suggest that there are fundamental differences between how microsatellite stable (MSS) and microsatellite unstable (MSI) rectal cancers should be managed. MSI patients, whilst only accounting for 2–3% of locally advanced rectal cancers (Muzny et al. 2012), do not respond well to neoadjuvant chemotherapy (Cercek et al. 2020). But, recent data showed that they can have dramatic responses to immune checkpoint inhibition with dostarlimab with 100% complete clinical response rate in a small 16-patient study (Cercek et al. 2022).

Radiation in Locally Recurrent Rectal Cancer

Locally recurrent rectal cancer is defined as recurrence of rectal cancer within the pelvis after previous surgical resection (Beyond TME Collaborative 2013). Rates can be up to 10% and the majority will have received neo-adjuvant (chemo) radiotherapy as part of initial multimodality treatment (Owens and Muirhead 2018; Valentini et al. 2011; Yu et al. 2008). Untreated, the median survival is six months (Guren et al. 2014). Patients often have significant morbidity and poor quality of life from pelvic pain, fistula, bleeding and fecal discharge (Räsänen et al. 2015).

Curative resection remains the most important factor for survival (Bouchard and Efron 2010; Guren et al. 2014). However, surgical resection, often a full pelvic exenteration, is associated with significant morbidity not always possible. Re-irradiation is emerging as an alternative therapeutic option and has been shown to have a significant palliative effect and favorable survival outcomes (Guren et al. 2014; Lee et al. 2019). Most evidence is for hyperfractionated treatment of between 1.2–1.5Gy per fraction, but in turn necessitates a high number of fractions and multiple visits (Mohiuddin et al. 2002, 2006). Stereotactic ablative body radiotherapy (SBRT), which involves very accurate delivery of a high radiation dose in a small number of fractions to a target with narrow margins (Guckenberger et al. 2014), can improve delivery, reduce off target effects and is potentially ideal for re-irradiation compared to standard fractionation (Murray et al. 2017) and limits the number of required visits. The evidence base to date for the use of SBRT in re-irradiation is limited for now to a small number case series (Johnstone et al. 2021; Lee et al. 2019; Smith et al. 2020) with generally acceptable toxicity using published cumulative constraints (Abusaris et al. 2012).

Radiation in "Extrapelvic" Colorectal Cancer

Approximately 20% of colorectal cancer (CRC) patients present with stage IV disease (Torre et al. 2015), while 20–30% will go on to develop metastatic disease (Grothey et al. 2018; Rödel et al. 2015). A proportion of these will have "oligometastatic disease" (Weichselbaum and Hellman 2011). The ESMO consensus guidelines for the management of patients with metastatic colorectal cancer, defines oligometastases as five or sometimes more metastases at two or three sites, primarily visceral and lymph nodes (Van Cutsem et al. 2016).

Metastasis directed therapy is increasingly used to treat metastatic disease sites to achieve durable benefit (Chua et al. 2012). This is best exemplified by surgical resection (Kanas et al. 2012), often in combination with systemic therapy (Nordlinger et al. 2008). Even aggressive management of unresectable liver disease using radiofrequency ablation (RFA) has demonstrated an overall survival benefit versus standard of care (Ruers et al. 2017), with similar findings noted for lung metastases (de Baère et al. 2015).

Data from large colorectal cohort studies using stereotactic ablative body radiotherapy (SBRT) in oligometastatic disease show high control rates of the treated metastases and overall survival rates of 75–80% at two years (Chalkidou et al. 2021;

Franzese et al. 2019; O'Cathail et al. 2020). The randomized phase II SABR-COMET trial demonstrated a survival benefit from the addition of stereotactic ablative body radiotherapy (SBRT) in oligometastatic disease at extra-cranial sites (Palma et al. 2019), where almost 20% of the patients had CRC. These data suggest that CRC patients with limited metastatic disease can derive significant benefit using advanced radiation techniques, mirroring that seen in resection and ablation.

Role of Adjuvant Chemotherapy after Pelvic Radiotherapy

The use of adjuvant chemotherapy in the contemporary management of rectal cancer is controversial. A 2012 Cochrane metanalysis of 21 randomized rectal trials showed a significant benefit in DFS and OS for patients in receipt of adjuvant fluoropyrimidine based chemotherapy, compared to observation alone (Petersen et al. 2012). However, the analyzed studies bear no relation to modern practice with no widespread TME surgery and selective adjuvant radiotherapy. In fact, only one trial used preoperative radiation.

To date, four randomized trials have been attempted to define the benefit of adjuvant chemotherapy – CAO/ARO/AIO-4 (Rödel et al. 2015), PETACC-6 (Schmoll et al. 2021), CHRONICLE (Glynne-Jones et al. 2014) and ADORE (Hong et al. 2019). Only one – ADORE – showed a significant improvement in the three-year disease free survival [HR 0.66, p = 0.05]. There are several reasons why these studies failed to demonstrate an improvement. Compliance is poor in the adjuvant setting, where only about 50% of patients complete a prescribed course. There may have been significant imbalances in baseline staging, where patients may have been over or under staged in relation to their nodal disease, for example. There may also be age-related factors. Patients under 61 in the AIO-04 derived significant benefit from adjuvant oxaliplatin while the median age in ADORE, the only positive trial, was 55 years old. Lastly, there are biological factors related to a patient's individual response to neoadjuvant radiotherapy which appear to be more prognostic than their stage at presentation, where those with an excellent response have three-year DFS of over 90% and poor responders have a corresponding survival of <60% (Fokas et al. 2017, 2018).

In summary, the data from available trials do not support routine use of adjuvant chemotherapy in rectal cancer after pelvic radiotherapy. However, younger patients with a high burden of residual pathological disease after resection are the most likely to derive some potential benefit following adequate counseling.

Key Management Messages

- Neoadjuvant radiotherapy for locally advanced rectal cancer is a key element in reducing local recurrence rates.
- Total Neoadjuvant Therapy (TNT), incorporating chemotherapy with radiation, is emerging as the optimum strategy to improve response rates, facilitate organ preservation and decrease distant metastatic disease.

Areas for Further Research

- A greater understanding of the biology underpinning radiation response and resistance is needed to develop predictive biomarkers and facilitate the successful incorporation of the novel therapies

Trusted Link for Further Reading

Rectal Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. https://doi.org/10.6004/jnccn.2022.0051

References

Abusaris, H., Hoogeman, M., and Nuyttens, J.J. (2012). Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. *Technol Cancer Res Treat* 11: 591–597. https://doi.org/10.7785/tcrt.2012.500261.

Bahadoer, R.R., Dijkstra, E.A., Etten, B.V. et al. (2021). Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 22: 29–42. https://doi.org/10.1016/S1470-2045(20)30555-6.

Benson, A.B., Venook, A.P., Al-Hawary, M.M. et al. (2022). Rectal cancer, version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 20: 1139–1167. https://doi.org/10.6004/jnccn.2022.0051.

Bosset, J.-F., Collette, L., Calais, G. et al. (2006). Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 355: 1114–1123. https://doi.org/10.1056/NEJMoa060829.

Bouchard, P. and Efron, J. (2010). Management of recurrent rectal cancer. *Ann Surg Oncol* 17: 1343–1356. https://doi.org/10.1245/s10434-009-0861-2.

Bujko, K., Wyrwicz, L., Rutkowski, A. et al. (2016). Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. *Ann Oncol* 27: 834–842. https://doi.org/10.1093/annonc/mdw062.

Cammà, C., Giunta, M., Fiorica, F. et al. (2000). Preoperative radiotherapy for resectable rectal cancera meta-analysis. *JAMA* 284: 1008–1015. https://doi.org/10.1001/jama.284.8.1008.

Cercek, A., Dos Santos Fernandes, G., Roxburgh, C.S. et al. (2020). Mismatch repair–deficient rectal cancer and resistance to neoadjuvant chemotherapy. *Clin Cancer Res* 26: 3271–3279. https://doi.org/10.1158/1078-0432.CCR-19-3728.

Cercek, A., Lumish, M., Sinopoli, J. et al. (2022). PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. *N Engl J Med* 386: 2363–2376. https://doi.org/10.1056/NEJMoa2201445.

Chalkidou, A., Macmillan, T., Grzeda, M.T. et al. (2021). Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study.

Lancet Oncol 22: 98–106. https://doi.org/10.1016/S1470-2045(20)30537-4 (accessed 9 June 2023).

Chua, T.C., Liauw, W., Chu, F., and Morris, D.L. (2012). Viewing metastatic colorectal cancer as a curable chronic disease. *Am J Clin Oncol* 35: 77. https://doi.org/10.1097/COC.0b013e3181fe4444.

Colorectal Cancer Collaborative Group. (2001). Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *Lancet* 358: 1291–1304. https://doi.org/10.1016/S0140-6736(01)06409-1 (accessed 9 June 2023).

Conroy, T., Bosset, J.-F., Etienne, P.-L. et al. (2021). Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 22: 702–715. https://doi.org/10.1016/S1470-2045(21)00079-6.

Beyond TME Collaborative. (2013). Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *BJS (Br J Surg)* 100: E1–E33. https://doi.org/10.1002/bjs.9192_1.

de Baère, T., Aupérin, A., Deschamps, F. et al. (2015). Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. *Ann Oncol* 26: 987–991. https://doi.org/10.1093/annonc/mdv037.

Fisher, B., Wolmark, N., Rockette, H. et al. (1988). Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-011. *J Natl Cancer Inst* 80: 21–29. https://doi.org/10.1093/jnci/80.1.21.

Fokas, E., Allgäuer, M., Polat, B. et al. (2019). Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. *JCO* 37: 3212–3222. https://doi.org/10.1200/JCO.19.00308.

Fokas, E., Fietkau, R., Hartmann, A. et al. (2018). Neoadjuvant rectal score as individual-level surrogate for disease-free survival in rectal cancer in the CAO/ARO/AIO-04 randomized phase III trial. *Ann Oncol* 29: 1521–1527. https://doi.org/10.1093/annonc/mdy143.

Fokas, E., Ströbel, P., Fietkau, R. et al. (2017). Tumor regression grading after preoperative chemoradiotherapy as a prognostic factor and individual-level surrogate for disease-free survival in rectal cancer. *J Natl Cancer Inst* 109. https://doi.org/10.1093/jnci/djx095.

Franzese, C., Comito, T., Toska, E. et al. (2019). Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy. *Radiother Oncol* 133: 220–226. https://doi.org/10.1016/j.radonc.2018.10.024.

Garcia-Aguilar, J., Chow, O.S., Smith, D.D. et al. (2015). Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol* 16: 957–966. https://doi.org/10.1016/S1470-2045(15)00004-2.

Garcia-Aguilar, J., Patil, S., Gollub, M.J. et al. (2022). Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *JCO* 40: 2546–2556. https://doi.org/10.1200/JCO.22.00032.

Gérard, J.-P., Conroy, T., Bonnetain, F. et al. (2006). Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *JCO* 24: 4620–4625. https://doi.org/10.1200/JCO.2006.06.7629.

Glimelius, B., Grönberg, H., Järhult, J. et al. (2003). A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncologica* 42: 476–492. https://doi.org/10.1080/02841860310012301.

Glynne-Jones, R., Counsell, N., Quirke, P. et al. (2014). Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 25: 1356–1362. https://doi.org/10.1093/annonc/mdu147.

Glynne-Jones, R., Wyrwicz, L., Tiret, E. et al. (2017). Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 28: iv22–iv40. https://doi.org/10.1093/annonc/mdx224.

Grothey, A., Sobrero, A.F., Shields, A.F. et al. (2018). Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 378: 1177–1188. https://doi.org/10.1056/NEJMoa1713709.

Guckenberger, M., Andratschke, N., Alheit, H. et al. (2014). Definition of stereotactic body radiotherapy. *Strahlenther Onkol* 190: 26–33. https://doi.org/10.1007/s00066-013-0450-y.

Guren, M.G., Undseth, C., Rekstad, B.L. et al. (2014). Reirradiation of locally recurrent rectal cancer: a systematic review. *Radiother Oncol* 113: 151–157. https://doi.org/10.1016/j.radonc.2014.11.021.

Hong, Y.S., Kim, S.Y., Lee, J.S. et al. (2019). Oxaliplatin-based adjuvant chemotherapy for rectal cancer after preoperative chemoradiotherapy (ADORE): long-term results of a randomized controlled trial. *JCO* 37: 3111–3123. https://doi.org/10.1200/JCO.19.00016.

Jin, J., Tang, Y., Hu, C. et al. (2022). Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). *JCO* JCO.21.01667. https://doi.org/10.1200/JCO.21.01667.

Johnstone, P., Okonta, L., Aitken, K. et al. (2021). A multicentre retrospective review of SABR reirradiation in rectal cancer recurrence. *Radiother Oncol* 162: 1–6. https://doi.org/10.1016/j.radonc.2021.06.030.

Kanas, G.P., Taylor, A., Primrose, J.N. et al. (2012). Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 4: 283–301. https://doi.org/10.2147/CLEP.S34285.

Lee, J., Kim, C.Y., Koom, W.S., and Rim, C.H. (2019). Practical effectiveness of re-irradiation with or without surgery for locoregional recurrence of rectal cancer: a meta-analysis and systematic review. *Radiother Oncol* 140: 10–19. https://doi.org/10.1016/j.radonc.2019.05.021.

Mohiuddin, M., Marks, G., and Marks, J. (2002). Long-term results of reirradiation for patients with recurrent rectal carcinoma. *Cancer* 95: 1144–1150. https://doi.org/10.1002/cncr.10799.

Mohiuddin, M., Winter, K., Mitchell, E. et al., Radiation Therapy Oncology Group Trial 0012, 2006. Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: radiation therapy oncology group trial 0012. *J Clin Oncol* 24, 650–655. https://doi.org/10.1200/JCO.2005.03.6095.

Murray, L.J., Lilley, J., Hawkins, M.A. et al. (2017). Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): a systematic review. *Radiother Oncol* 125: 213–222. https://doi.org/10.1016/j.radonc.2017.09.030.

Muzny, D.M., Bainbridge, M.N., Chang, K. et al., 2012. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 487, 330–337. https://doi.org/10.1038/nature11252.

Nordlinger, B., Sorbye, H., Glimelius, B. et al. (2008). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 371: 1007–1016. https://doi.org/10.1016/S0140-6736(08)60455-9 (accessed 9 June 2023).

O'Cathail, S.M., Smith, T., Owens, R. et al. (2020). Superior outcomes of nodal metastases compared to visceral sites in oligometastatic colorectal cancer treated with stereotactic ablative radiotherapy. *Radiother Oncol*. https://doi.org/10.1016/j.radonc.2020.08.012.

Owens, R. and Muirhead, R. (2018). External beam re-irradiation in rectal cancer. *Clin Oncol Re-irradiation* 30: 116–123. https://doi.org/10.1016/j.clon.2017.11.009.

Palma, D.A., Olson, R., Harrow, S. et al. (2019). Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 393: 2051–2058. https://doi.org/10.1016/S0140-6736(18)32487-5 (accessed 9 June 2023).

Perez, K., Safran, H., Sikov, W. et al. (2017). Complete neoadjuvant treatment for rectal cancer: the brown university oncology group CONTRE study. *Am J Clin Oncol* 40: 283–287. https://doi.org/10.1097/COC.0000000000000149.

Petersen, S.H., Harling, H., Kirkeby, L.T. et al. (2012). Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012: CD004078. https://doi.org/10.1002/14651858.CD004078.pub2.

Räsänen, M., Carpelan-Holmström, M., Mustonen, H. et al. (2015). Pattern of rectal cancer recurrence after curative surgery. *Int J Colorectal Dis* 30: 775–785. https://doi.org/10.1007/s00384-015-2182-1.

Rödel, C., Graeven, U., Fietkau, R. et al. (2015). Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 16: 979–989. https://doi.org/10.1016/S1470-2045(15)00159-x (accessed 9 June 2023).

Ruers, T., Van Coevorden, F., Punt, C.J.A. et al. (2017). Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 109. https://doi.org/10.1093/jnci/djx015.

Schmoll, H.-J., Stein, A., Van Cutsem, E. et al. (2021). Pre- and postoperative capecitabine without or with oxaliplatin in locally advanced rectal cancer: PETACC 6 trial by EORTC GITCG and ROG, AIO, AGITG, BGDO, and FFCD. *JCO* 39: 17–29. https://doi.org/10.1200/JCO.20.01740.

Smith, T., O'Cathail, S.M., Silverman, S. et al. (2020). Stereotactic body radiation therapy reirradiation for locally recurrent rectal cancer: outcomes and toxicity. *Adv Radiat Oncol* 5: 1311–1319. https://doi.org/10.1016/j.adro.2020.07.017.

Torre, L.A., Bray, F., Siegel, R.L. et al. (2015). Global cancer statistics, 2012. *CA Cancer J Clin* 65: 87–108. https://doi.org/10.3322/caac.21262.

Valentini, V., van Stiphout, R.G.P.M., Lammering, G. et al. (2011). Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *JCO* 29: 3163–3172. https://doi.org/10.1200/JCO.2010.33.1595.

Van Cutsem, E., Cervantes, A., Adam, R. et al. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27: 1386–1422. https://doi.org/10.1093/annonc/mdw235.

Weichselbaum, R.R. and Hellman, S. (2011). Oligometastases revisited. *Nat Rev Clin Oncol* 8: 378–382. https://doi.org/10.1038/nrclinonc.2011.44.

Yu, T.-K., Bhosale, P.R., Crane, C.H. et al. (2008). Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer. *Int J Radiat Oncol Biol Phys* 71: 1175–1180. https://doi.org/10.1016/j.ijrobp.2007.11.018.

Chemotherapy, Radiotherapy and Biological/Immunological Therapy for Colorectal Cancer

Chemotherapy Section Overview

Magdalena Krakowska

Adjuvant Chemotherapy of Colon Cancer

Rationale

The adjuvant chemotherapy is used in patients with colon cancer after curative resection. Its aim is to eradicate occult micrometastases and thereby increase the probability of cure. The absolute benefit of postoperative treatment is greater in patients at higher risk of recurrence.

Indications

Adjuvant chemotherapy is the standard of care for patients with stage III disease. It is also recommended for patients with stage II disease with poor prognostic features:

- pT4 tumors
- poorly differentiated/undifferentiated histology
- lymphovascular invasion
- perineural invasion
- bowel obstruction
- perforation of lesion
- indeterminate or positive margins
- inadequately sampled lymph nodes (< 12)

High microsatellite instability is associated with better prognosis, and may limit indications for adjuvant chemotherapy in stage II disease. Decision-making regarding the use of adjuvant therapy should take into account patient's opinion, comorbidities, and potential toxicities associated with treatment.

Adjuvant Regimens

Adjuvant chemotherapy with fluorouracil (5-FU) and folinic acid (leucovorin, LV) improves five-year DFS rate by 17%, and five-year OS by approximately 14% for patients with stage III disease. In stage II colon cancer, the benefit limited to DFS is approximately 4% (Gill et al. 2004). Infusional 5-FU/LV is better tolerated than given in injection. Capecitabine is the oral fluoropyrimidine prodrug. For patients with stage III, capecitabine was noninferior to 5-FU/LV with respect to DFS and OS (Twelves et al. 2012).

Adding oxaliplatin to fluoropyrimidine in patients with stage III colon cancer further improves 5-year DFS by 7–8% and OS by 4–6%. No statistically significant difference was observed for stage II patients (André et al. 2015). The benefit of the addition of oxaliplatin in patients 70 years of age or older has not been proven.

There are no data to support the use of irinotecan, or other cytotoxic agents, in the adjuvant treatment of colon cancer.

Duration of Adjuvant Therapy

The usual duration of treatment is six months. Prolonged oxaliplatin exposure is associated with neurotoxicity, which can be persistent. The IDEA collaboration (6 randomized phase III trials) investigated whether the reduction of the adjuvant chemotherapy to three months of FOLFOX (oxaliplatin, 5-FU, LV) or CAPOX (oxaliplatin, capecitabine) would deteriorate DFS. IDEA failed to demonstrate the noninferiority of shorter treatment in overall population. However, in the exploratory analysis of patients treated with CAPOX, DFS was noninferior, especially in the low-risk (T1-3, N1) group (André et al. 2020).

Perioperative Chemotherapy for Resectable Metastatic Disease

The optimal sequence of resection and chemotherapy remains unclear. In the phase III trial, there was no difference in PFS or OS with the addition of the perioperative FOLFOX4 chemotherapy compared with surgery alone in the intent-to-treat population. The modest benefit in PFS was observed only for patients, who actually initiated treatment (Nordlinger et al. 2013). Meta-analysis also found that adding systemic therapy to resections improves only DFS but not OS (Khoo et al. 2016). However, the neoadjuvant or adjuvant chemotherapy is usually considered for most patients undergoing metastasis resection because of the high risk of relapse in this population. The total perioperative treatment should last six months.

Chemotherapy for Advanced or Metastatic Disease

Rationale

Approximately 50–60% of patients with colorectal cancer develop metastases, most often in the liver. Patients with resectable disease, especially with liver or lung metastases, are obvious candidates for radical surgery. For all others at stage IV disease, the systemic treatment is standard of care, because it prolongs survival and improves quality of life. The mainstay of systemic treatment remains chemotherapy most often combined with a biologic agent (e.g. bevacizumab, cetuximab, panitumumab).

First-line Therapy

Fluoropyrimidine Monotherapy

An intravenous continuous infusion is a standard way of 5-FU administration as it resulted in a higher response rate than when administered as an injection (22 vs 14%), and in a slight survival benefit (relative risk of death lower by 12%). Infusional 5-FU also had a more favorable toxicity profile, caused less hematologic adverse events (4% vs 31%), but more hand-foot skin reactions (34% vs. 13%) (Piedbois et al. 1998). Capecitabine was shown to be equivalent to bolus 5-FU with respect to PFS or OS and demonstrated higher response rates (26% vs. 16%) (Hoff et al. 2001). Infusional 5-FU/LV or capecitabine (fluoropyrimidine monotherapy) is currently recommended for patients not eligible for more intensive therapy.

Irinotecan-based Therapy

The addition of irinotecan to 5-FU improves response rate and survival. The median PFS of patients treated with FOLFIRI (irinotecan, 5-FU, LV) regimen is 7 to 9 months and response rate achieves 30–40%. Adverse events associated with irinotecan include diarrhea, vomiting, alopecia and severe neutropenia. Irinotecan combined with capecitabine showed worse PFS than in combination with 5-FU, and was more toxic (severe vomiting, diarrhea, dehydration) (Fuchs 2007).

Oxaliplatin-based Therapy

FOLFOX and FOLFIRI are considered to be equally effective in first line treatment. In the phase III trial, there was no difference in response rate, PFS, and OS. Median OS was 14 months for patients receiving FOLFIRI, compared with 15 months for patients treated with FOLFOX (Colucci et al. 2005). The difference between these two regimens is mainly in the toxicity profile. Thrombocytopenia and neurotoxicity were more common in oxaliplatin-treated group, whereas diarrhea, hair loss, nausea, and vomiting were more common in FOLFIRI-treated group. CAPOX and FOLFOX provides similar benefits for patients with metastatic disease. No differences in PFS and OS were observed. CAPOX was associated with more diarrhea and hand-foot syndrome than FOLFOX (Cassidy et al. 2008). The chemotherapy triplet FOLFOXIRI (oxaliplatin, irinotecan, 5-FU, LV) compared with FOLFIRI was associated with an increased toxicity, the impact on response rate, PFS and OS was inconsistent (Falcone et al. 2007; Souglakos et al. 2006).

De-escalation Strategy

Interest in de-escalation approach is growing due to the reduction of toxicity and the possible improvement of the quality of life. In general, this strategy involves intensive first-line treatment, followed by less intensive maintenance therapy or chemotherapy-free intervals.

Results of the OPTIMOX1 trial, which compared 6 cycles of FOLFOX7 followed by maintenance treatment without oxaliplatin for 12 cycles, and then reintroduction of FOLFOX7 with continuous FOLFOX4, showed no differences in PFS or OS (Tournigand et al. 2006). Oxaliplatin-free intervals resulted in decreased neurotoxicity. Based on the phase III trial results, intermittent chemotherapy with FOLFIRI (treatment for 2 months alternating with the same duration of breaks) was non-inferior to continuous treatment (Labianca et al. 2011).

Table 1 Commonly used chemotherapy regimens for patients with colorectal cancer.

Regimen	Drug	Interval
LVFU2	folinic acid 200 mg/m^2 IV infusion days 1 and 2 fluorouracil 400 mg/m^2 IV bolus days 1 and 2 fluorouracil 600 mg/m^2 IV 22 hours continuous infusion days 1 and 2	2 weeks
capecitabine	capecitabine 1000–1250 mg/m^2 PO twice daily for 14 days	3 weeks
FOLFOX4	oxaliplatin 85 mg/m^2 IV day 1 folinic acid 200 mg/m^2 IV infusion days 1 and 2 fluorouracil 400 mg/m^2 IV bolus days 1 and 2 fluorouracil 600 mg/m^2 IV 22 hours continuous infusion days 1 and 2	2 weeks
CAPOX	oxaliplatin 130 mg/m^2 IV day 1 capecitabine 1000 mg/m^2 PO twice daily for 14 days	3 weeks
FOLFIRI	irinotecan 180 mg/m^2 IV day 1 folinic acid 400 mg/m^2 IV infusion day 1 fluorouracil 400 mg/m^2 IV bolus day 1, followed by 2400 mg/m^2 46 hours continuous infusion	2 weeks

It is unclear whether discontinuation of all chemotherapy until tumor progression will not diminish the efficacy of treatment. Several trials demonstrated that this strategy had a detrimental impact on PFS and probably on OS. However, discontinuation of chemotherapy could be reasonable for patients with long-lasting response to treatment or clinically significant toxicity.

Second-line or Subsequent Therapy

Decisions regarding treatment after progression depend on the type and timing of previous therapies, and the toxicity. After oxaliplatin-based therapy, it is recommended to use the irinotecan-based regimen in second line, and vice versa. Based on the results of GERCOR trial, both sequences resulted in similar efficacy (Tournigand et al. 2004). Second line chemotherapy with oxaliplatin is associated with increased response rate but without impact on survival compared with irinotecan-based treatment.

Irinotecan, in contrast to oxaliplatin, can be also administered in monotherapy, especially in patients with contradiction to 5-FU.

Trifluridine-tipiracil is an oral combination drug that provided benefit in subsequent lines of therapy. Results of the phase III study comparing trifluridine-tipiracil with placebo after progression on at least two prior regimens showed improvement in PFS and OS (Mayer et al. 2015).

The most commonly used chemotherapy regimens are presented in Table 1.

Key Take Home Messages

1 Adjuvant oxaliplatin-based chemotherapy improves the five-year OS rate up to 20% in patients with stage III colon cancer.
2 Addition of oxaliplatin or irinotecan to fluoropyrimidine in unresectable, metastatic colorectal cancer mainly increases response rate and PFS.
3 Pre-planned strategy of using all active drugs allows the greatest improvement in OS for patients with unresectable, metastatic colorectal cancer.

Knowledge Gap

1 Strategies for overcoming resistance to systemic treatment.

Trusted Websites for Further Reading

1 https://www.esmo.org
2 https://asco.org
3 https://www.nccn.org

References

André, T., de Gramont, A., Vernerey, D. et al. (2015). Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol* 33: 4176–4187. https://doi.org/10.1200/JCO.2015.63.4238.

André, T., Meyerhardt, J., Iveson, T. et al. (2020). Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. *Lancet Oncol* 21: 1620–1629. https://doi.org/10.1016/S1470-2045(20)30527-1.

Cassidy, J., Clarke, S., Díaz-Rubio, E. et al. (2008). Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 26: 2006–2012. https://doi.org/10.1200/JCO.2007.14.9898.

Colucci, G., Gebbia, V., Paoletti, G. et al. (2005). Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 23: 4866–4875. https://doi.org/10.1200/JCO.2005.07.113.

Falcone, A., Ricci, S., Brunetti, I. et al. (2007). Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 25: 1670–1676. https://doi.org/10.1200/JCO.2006.09.0928.

Fuchs, C.S., Marshall, J., Mitchell, E. et al. (2007). Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 25: 4779–4786. https://doi.org/10.1200/JCO.2007.11.3357.

Gill, S., Loprinzi, C.L., Sargent, D.J. et al. (2004). Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol* 22: 1797–1806. https://doi.org/10.1200/JCO.2004.09.059.

Hoff, P.M., Ansari, R., Batist, G. et al. (2001). Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 19: 2282–2292. https://doi.org/10.1200/JCO.2001.19.8.2282.

Khoo, E., O'Neill, S., Brown, E. et al. (2016). Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. *HPB (Oxford)* 18: 485–493. https://doi.org/10.1016/j.hpb.2016.03.001.

Labianca, R., Sobrero, A., Isa, L. et al. (2011). Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. *Ann Oncol* 22: 1236–1242. https://doi.org/10.1093/annonc/mdq580.

Mayer, R.J., Van Cutsem, E., Falcone, A. et al. (2015). Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 372: 1909–1919. https://doi.org/10.1056/NEJMoa1414325.

Nordlinger, B., Sorbye, H., Glimelius, B. et al. (2013). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 14: 1208–1215. https://doi.org/10.1016/S1470-2045(13)70447-9.

Piedbois, P., Rougier, P., Buyse, M. et al. (1998). Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 16: 301–308. https://doi.org/10.1200/JCO.1998.16.1.301.

Souglakos, J., Androulakis, N., Syrigos, K. et al. (2006). FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 94: 798–805. https://doi.org/10.1038/sj.bjc.6603011.

Tournigand, C., André, T., Achille, E. et al. (2004). FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 22: 229–237. https://doi.org/10.1200/JCO.2004.05.113.

Tournigand, C., Cervantes, A., Figer, A. et al. (2006). OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol* 24: 394–400. https://doi.org/10.1200/JCO.2005.03.0106.

Twelves, C., Scheithauer, W., McKendrick, J. et al. (2012). Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. *Ann Oncol* 23: 1190–1197. https://doi.org/10.1093/annonc/mdr366.

Biologic and Immunotherapy for Colorectal Cancer

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History of Biological Therapy for CRC

While the history of biologic (or molecularly targeted) therapy and immunotherapy for colorectal cancer (CRC) is somewhat shorter than that of cytotoxic chemotherapy and radiotherapy, these agents have established themselves as an essential part of the therapeutic armamentarium in this disease. With the exception of early, arguably disappointing, vaccine studies, biologics and immunotherapeutics really came of age in the 2000s following advances in molecular biology and methods for production of monoclonal antibodies at therapeutic scale.

Biologics for CRC

The identification in 1978 of the epidermal growth factor receptor (EGFR) as a critical regulator of intracellular signaling and cell growth, survival and migration (Gschwind et al. 2004) stimulated research into its role in cancer. Aberrant EGFR expression was found in multiple cancer types including 25–77% of CRC (Xie et al. 2020). Cetuximab, a chimeric monoclonal antibody against EGFR, was the first targeted agent approved for CRC by the US Food and Drug Administration (FDA) in 2004 (Xie et al. 2020), based on prolongation of progression-free survival (PFS) in patients with metastatic CRC (mCRC) refractory to irinotecan (Cunningham et al. 2004). Subsequent studies demonstrated that the addition of cetuximab or the alternative anti-EGFR monoclonal panitumumab to first line chemotherapy improves clinical outcome in mCRC (Jonker et al. 2007), although this benefit is limited to patients with tumors lacking mutations in *KRAS*, *NRAS* and to a lesser extent *BRAF* (Karapetis et al. 2008). Although the importance of angiogenesis in promoting tumor growth, invasion and metastasis has long been recognized, the identification of the vascular endothelial growth factor (VEGF) family as mediators of this provided a rational therapeutic target. A landmark trial published in 2004 demonstrated that the addition of the anti-VEGF monoclonal bevacizumab to irinotecan-based chemotherapy improved PFS and overall survival (OS) in mCRC (Hurwitz et al. 2004) and led to FDA approval for this indication. While a subsequent study showed more modest benefit for bevacizumab in combination with first-line oxaliplatin-based chemotherapy, the chemo-bevacizumab doublet has established itself as a standard of care for mCRC. From these data, one may reasonably ask how clinicians should decide between anti-EGFR and anti-VEGF therapy for their patients with mCRC? Data accumulated over the last decade, including a meta-analysis have revealed that chemotherapy plus anti-EGFR therapy is superior to chemotherapy plus anti-VEGF therapy in patients with *RAS*/*BRAF*-wild-type tumors arising on the left-side of the colon (i.e. distal to the transverse colon), while chemotherapy plus an anti-VEGF monoclonal is preferable for patients with RAS/BRAF mutant tumors or those with right-sided primary tumor (Khattak et al. 2015). While it has been postulated that the association of treatment (dis)benefit with primary tumor location relates to the embryological derivation of the right and left side of the colon (Boeckx et al. 2018; Yamashita et al. 2018), there are other plausible explanations, including difference in the intestinal microbiome, and the prevalence of other molecular alterations such as mutations in *PIK3CA*, and amplification of HER2 and other possible determinants of anti-EGFR sensitivity (Bertotti et al. 2015; Mei et al. 2016; Seo et al. 2014). While *BRAF* mutation predicts resistance to anti-EGFR therapy alone or in combination with cytotoxics, the development of specific inhibitors of the most common *BRAF* mutation (V600E, present in ~10% of mCRCs) permitted rational targeting in this patient subgroup. The BEACON study showed that a combination of either a triplet of a BRAF inhibitor (encorafenib), cetuximab and a MEK1/2 inhibitor (bimimetinib) or the encorafenib and cetuximab doublet were highly active against *BRAF* V600E-mutant mCRC as second line treatment, with significantly superior OS to chemotherapy (Kopetz et al. 2019). As the doublet had near-identical efficacy to the triplet, but with less toxicity, this has established itself as preferred therapy for this patient subgroup; a trial in first line therapy is underway. Importantly, the encorafenib and cetuximab doublet is the first biologic-only regimen licensed in mCRC by the FDA. Other biologics to have established roles in mCRC include regorafenib, a tyrosine kinase inhibitor (TKI) with multiple targets for third line therapy (Grothey et al. 2013; Van Cutsem et al. 2016) and agents targeting ERBB2/HER2 for the 3% of CRCs with ERBB2/HER2 amplification (Sartore-Bianchi et al. 2019). Soberingly, despite their activity in metastatic disease, both anti-EGFR and anti-VEGF therapies have failed to improve outcomes in early-stage CRC as adjuvant therapy (Allegra et al. 2011; De Gramont et al., 2012; Kerr et al. 2016). The reasons for this are not fully understood, but these findings certainly advocate for caution when extrapolating activity in the metastatic setting to earlier in the disease course.

Immunotherapy for CRC

As with biologics, the development of immune checkpoint inhibitors (ICI) derives from painstaking preclinical studies demonstrating the role of CTLA4 and PD1 in inhibiting the T cell response in the setting of chronic antigen stimulation (Robert 2020). Given that it was well recognized that the density of lymphocytic infiltrate correlated with better outcome in CRC (Galon et al. 2006), the use of ICI in metastatic CRC – where the immune response is self-evidently incapable of preventing tumor growth – was a logical avenue to pursue. However, in contrast to melanomas and lung cancer, for most CRCs, these drugs failed to show meaningful activity as monotherapy or in combination with chemotherapy in most cases (Brahmer et al. 2012). There was, however a stunning exception; the subgroup of 4% of mCRCs with deficiency in DNA mismatch repair (dMMR) which showed profound, and in many cases prolonged responses (Le et al. 2015; Overman et al. 2017). Indeed, for this subgroup, ICIs also offer a more tolerable toxicity profile compared to chemotherapy. Consequently, anti-PD1 therapy in the form of nivolumab or pembrolizumab gained FDA approval for this indication in 2017, and is now preferred over chemotherapy for first line therapy by many clinicians. The most plausible explanation for the responsiveness of dMMR CRCs to ICI is that their elevated mutation rate causes an abundance of non-self peptides which are recognized by re-activated T cells. Understanding whether the failure of ICI in CRCs with proficient MMR relates to their lower mutation burden or other factors is an area of active investigation, as is the use of combination treatment, including immunotherapy-biologic and other immunomodulatory compounds (Lote et al. 2022). In contrast to the seemingly reduced efficacy of biologics in early-stage disease, emerging data indicate that activity of ICI is significantly greater in early-stage dMMR CRC. Exemplars include a prospective phase II study, in which six months of Dostarlizumab (anti-PD-1) resulted in prolonged clinical complete response (CR) for locally advanced dMMR CRC in all patients (Cercek et al. 2022), the PICC trial in which six months of Toripalimab (anti-PD-1) plus celecoxib (COX-2 inhibitor) in locally advanced dMMR CRC resulted in a complete pathological response in 88% of patients (Hu et al. 2022), and the NICHE and NICHE-2 trials, where in the latter 6 weeks of neoadjuvant ICI resulted in pathological CR in 67% of dMMR tumors (Chalabi et al. 2020). These studies pave the way to organ-sparing approaches in dMMR CRC – something which until recently was considered unfeasible.

Summary

In summary, during the last two decades' biologics have established themselves as standards of care in mCRC, while immunotherapy has emerged as the treatment of choice for dMMR mCRC and is near-certain to become the same in early-stage dMMR tumors. While the failure of anti-EGFR and anti-VEGF therapies in early-stage disease militates caution, the pace of advance in biological understanding and therapeutic targeting means we can be sanguine about the improvements biologics and immunotherapeutics will deliver for our patients during the next twenty years. In addition to new targets and drug combinations, future work should aim to rationalize the use of these drugs to the patients most likely to benefit, as the substantial costs of these agents poses a challenge for even the best-funded healthcare systems (Weng et al. 2022).

Key Management Messages

- The addition of anti-EGFR or anti-VEGF biologics to chemotherapy improves survival in mCRC; the choice of which to use depends on *RAS*/*BRAF* mutation status and primary tumor location.
- Anti-EGFR and anti-VEGF therapy have no role in adjuvant therapy.
- Immune checkpoint inhibition has unprecedented activity in DNA mismatch repair deficient (dMMR) mCRC and offers possibility of organ-sparing therapy in localized disease.

Areas for Further Research

- Development and application of novel molecularly-targeted therapies in mCRC
- Combination strategies to sensitize resistant mismatch repair proficient (pMMR) CRCs to immunotherapy

Trusted Links for Further Reading

- ESMO guidelines for metastatic colorectal cancer
- Review of biologics for colorectal cancer

References

Allegra, C.J., Yothers, G., O'connell, M.J. et al. (2011). Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol* 29: 11–16.

Bertotti, A., Papp, E., Jones, S. et al. (2015). The genomic landscape of response to EGFR blockade in colorectal cancer. *Nature* 526: 263–267.

Boeckx, N., Janssens, K., Van Camp, G. et al. (2018). The predictive value of primary tumor location in patients with metastatic colorectal cancer: a systematic review. *Crit Rev Oncol Hematol* 121: 1–10.

Brahmer, J.R., Tykodi, S.S., Chow, L.Q.M. et al. (2012). Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 366: 2455–2465.

Cercek, A., Lumish, M., Sinopoli, J. et al. (2022). PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. *N Engl J Med* 386: 2654–2666.

Chalabi, M., Fanchi, L.F., Dijkstra, K.K. et al. (2020). Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 26: 566–576.

Cunningham, D., Humblet, Y., Siena, S. et al. (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351: 337–345.

De Gramont, A., Van Cutsem, E., Schmoll, H.J. et al. (2012). Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol* 13: 1225–1233.

Galon, J., Costes, A., Sanchez-cabo, F. et al. (2006). Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 313: 1960–1964.

Grothey, A., Van Cutsem, E., Sobrero, A. et al. (2013). Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 381: 303–312.

Gschwind, A., Fischer, O.M., and Ullrich, A. (2004). The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev Cancer* 4: 361–370.

Hu, H., Kang, L., Zhang, J. et al. (2022). Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol* 7: 38–48.

Hurwitz, H., Fehrenbacher, L., Novotny, W. et al. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350: 2335–2342.

Jonker, D.J., O'Callaghan, C.J., Karapetis, C.S. et al. (2007). Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 357: 2040–2048.

Karapetis, C.S., Khambata-ford, S., Jonker, D.J. et al. (2008). K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 359: 1757–1765.

Kerr, R.S., Love, S., Segelov, E. et al. (2016). Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. *Lancet Oncol* 17: 1543–1557.

Khattak, M.A., Martin, H., Davidson, A., and Phillips, M. (2015). Role of first-line anti-epidermal growth factor receptor therapy compared with anti-vascular endothelial growth factor therapy in advanced colorectal cancer: a meta-analysis of randomized clinical trials. *Clin Colorectal Cancer* 14: 81–90.

Kopetz, S., Grothey, A., Yaeger, R. et al. (2019). Encorafenib, binimetinib, and cetuximab in *BRAF* V600E–mutated colorectal cancer. *N Engl J Med* 381: 1632–1643.

Le, D.T., Uram, J.N., Wang, H. et al. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 372: 2509–2520.

Lote, H., Starling, N., Pihlak, R., and Gerlinger, M. (2022). Advances in immunotherapy for MMR proficient colorectal cancer. *Cancer Treat Rev* 111: 102480.

Mei, Z.B., Duan, C.Y., Li, C.B. et al. (2016). Prognostic role of tumor PIK3CA mutation in colorectal cancer: a systematic review and meta-analysis. *Ann Oncol* 27: 1836–1848.

Overman, M.J., Mcdermott, R., Leach, J.L. et al. (2017). Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 18: 1182–1191.

Robert, C. (2020). A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun* 11.

Sartore-Bianchi, A., Amatu, A., Porcu, L. et al. (2019). HER2 positivity predicts unresponsiveness to EGFR-targeted treatment in metastatic colorectal cancer. *Oncologist* 24: 1395–1402.

Seo, A.N., Kwak, Y., Kim, D.-W. et al. (2014). HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. *PLoS ONE* 9: e98528.

Van Cutsem, E., Cervantes, A., Adam, R. et al. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27: 1386–1422.

Weng, J., Li, S., Zhu, Z. et al. (2022). Exploring immunotherapy in colorectal cancer. *J Hematol Oncol* 15.

Xie, Y.-H., Chen, Y.-X., and Fang, J.-Y. (2020). Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct Target Ther* 5.

Yamashita, S., Brudvik, K.W., Kopetz, S.E. et al. (2018). Embryonic origin of primary colon cancer predicts pathologic response and survival in patients undergoing resection for colon cancer liver metastases. *Ann Surg* 267: 514–520.

Answers to Case Scenarios

Jeremy Meyer & Justin Davies

Case 1: Sporadic Localized Right Colon Cancer

For the management of colon cancer, routine staging modalities include a complete colonoscopy, aimed at confirming the nature of the tumor, tattooing the lesion distal to the tumor in at least 2 separate places and ruling out any synchronous colorectal cancer (which can occur in 2–3% of patients, with a higher incidence in cases of hereditary colorectal cancer). Moreover, a CT of the chest, abdomen and pelvis should be performed to clinically stage the tumor in terms of assessing for distant metastases, and to allow assessment of local resectability with optimal planning of the surgical strategy. This staging should be tailored to the patient, and more imaging modalities (for example a PET-CT, a liver MRI) can be added in case metastatic disease is suspected (Argiles et al. 2020).

In the case scenario, the lesion was staged as being cT3 N2 M0. Ideally, the patient should be entered into an enhanced recovery after surgery (ERAS) protocol (Gustafsson et al. 2019; Moran et al. 2017). The surgical approach should be tailored to the patient and the surgeon's expertise, and can consist of open right hemicolectomy, laparoscopic right hemicolectomy or robotic right hemicolectomy. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) Guideline recommends choosing the laparoscopic approach over the open approach whenever possible (Moran et al. 2017), due to its similar operative specimen and oncological outcomes but short-term benefits in terms of post-operative pain, blood loss and length of stay (Jayne et al. 2007; Kennedy et al. 2014). The minimally invasive approach almost invariably includes the dissection of the right colon along the anatomical planes, but sometimes bowel division, vessel division and anastomosis creation are performed extra-corporeally through the incision made for the specimen extraction due to technical challenges. Robotic surgery may allow performing most of these procedures intra-corporeally, and may potentially bring benefits in terms of length of specimen extraction site. Finally, some surgeons advocate performing complete mesocolic excision (CME) for right-sided colon cancer. CME was introduced by Hohenberger in 2009 to improve oncological outcomes of right colectomy by transposing the lessons learned from total mesorectal excision (TME) to colon cancer (Hohenberger et al. 2009). CME aims at completely removing the mesocolon and its lymph nodes (corresponding to a Japanese D3 lymphadenectomy) and can be summarized in three principles: 1. sharp dissection respecting the embryological planes (to remove D1, D2 and D3 lymph nodes), 2. central vascular ligation (to remove D3 lymph nodes) and 3. sufficient bowel resection (to remove pericolic lymph nodes). So far, the potential benefits of the technique have not been demonstrated by randomized controlled trials and vascular complications have been reported (Xu et al. 2021). The ACPGBI recommends additional evidence of the benefits of CME before its routine adoption (Moran et al. 2017)

The case scenario depicts a patient with Union for International Cancer Control (UICC) stage III colon cancer who has been recommended consideration of adjuvant chemotherapy by the multidisciplinary team. The rationale for use of adjuvant chemotherapy in colon cancer is to eradicate micrometastatic disease in draining lymph nodes that were not removed by the surgical procedure and any other micrometastatic diases not detected on routine imaging. Current recommendations of the European Society for Medical Oncology (ESMO) stipulate that patients with UICC stage III colon cancer (Node positive) should be offered adjuvant chemotherapy to reduce the risk of recurrence and improve overall survival (Argiles et al. 2020). Chemotherapy usually consists of a combination of fluoropyrimidine and oxaliplatin, as the addition of oxaliplatin to fluoropyrimidine brings a disease-free survival benefit (Andre et al. 2004; Yothers et al. 2011). Based on the IDEA study, both 6-month FOLFOX (a combination of folinic acid, 5-FU and oxaliplatin) and 3 to 6-month CAPOX (a combination of capecitabin and oxaliplatin) constitute the current standard of care (Grothey et al. 2018), including recently updated National Institute for Health and Care Excellence (NICE) Guidelines for Colorectal Cancer in United Kingdom (NIfHaCE 2020). The benefit of chemotherapy in terms of survival in patients with UICC stage II (T3-T4 N0) cancer is less clear, but chemotherapy can be proposed to intermediate and high-risk patients (Argiles et al. 2020). The level of risk is estimated based on the number of lymph nodes harvested (<12 constitutes high risk), a pT4 stage including perforation, the histological subtype and grading of the cancer, the presence of lymphatic or vascular or perineural invasion, lymphoid inflammatory response, involvement of resection margins and serum pre-operative CEA (Argiles et al. 2020).

After treatment for colon cancer with curative intent, follow-up should be performed for early detection of eventual local recurrence and metachronous metastatic disease. Most recurrences occur during the first 3 years of follow-up, and a small proportion happen between years 3 and year 5. Therefore, it is commonly agreed that follow-up should be performed during the first 3–5 years after curative treatment for colon cancer (Argiles et al. 2020). However, as highlighted by the European Society for Coloproctology (ESCP), national guidelines for follow-up are heterogeneous (Bastiaenen et al. 2019). Nevertheless, the ESMO recommends performing physical examination and CEA level every 3–6 months for the first 3 years, and every 6 months thereafter until year 5. Colonoscopy should be performed at year 1, and every 3–5 years thereafter. CT of the abdomen and chest should be performed every 6–12 months for the first three years for patients at higher risk (Argiles et al. 2020), who are usually defined as patients above UICC stage I. NICE has similar recommendations for the first 3 years of follow up, with colonoscopic surveillance recommended by Guidelines from the British Society of Gastroenterology and generally recommending a colonoscopy at 1 year after resection, and then at 3 years, with surveillance after that depending on the colonoscopic findings (Rutter et al. 2020).

Case 2: Prophylactic Surgery for Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is defined as the presence of multiple adenomas (>100 in the classical phenotype and 10–100 in the attenuated phenotype) localized in the colon and rectum of affected individuals. The syndrome has an autosomal dominant transmission, a 100% penetrance and is associated with a germline mutation of the APC gene. The APC gene is a tumor suppressor gene which regulates epithelial growth. FAP is associated with a wide range of cancers, but is commonly associated with non-adenomatous gastric polyps, adenomatous duodenal polyps and desmoid tumors, which constitute an important cause of mortality in patients after proctocolectomy. Considering the important risk of early colorectal cancer in patients suffering from FAP, yearly endoscopic follow-up is started from age 12–15 years, and prophylactic surgery is generally offered before the age of 25 (Stjepanovic et al. 2019). Surgical options include initial subtotal colectomy and end ileostomy (continent or not), subtotal colectomy and ileo-rectal anastomosis, procto-colectomy and end ileostomy (continent or not), or procto-colectomy with ileo-anal pouch anastomosis. The extent of resection (subtotal colectomy or procto-colectomy with/without mucosectomy; proctectomy can also preserve the anal canal or not) depends on the estimated risk of metachronous cancer in the residual rectum (or residual rectal mucosa), patient's compliance with future follow-up and patient's wishes regarding preservation of sexual function. The risk can be estimated depending on the number of polyps in the rectum (>20 polyps in the last 10 cm constitutes a higher risk) and depending on the mutated codon in the APC gene. The decision to proceed to a restoration of continuity (ileo-rectal anastomosis or ileo-anal pouch) depends on many factors, including the sphincter function, the risk of anastomotic leak and patient's expectations.

In the example provided, mutation in the codon 1309 exposes the patient to a higher risk of rectal cancer (Ficari et al. 2000). Therefore, the optimal surgical procedure was a proctocolectomy, with end ileostomy or creation of an ileo-anal pouch as a quality of life decision for the patient. Ileo-anal pouch anastomosis is at risk for anastomotic leak. Therefore, it is a common practice to divert the faecal stream with a temporary loop ilestomy. This could have been associated with a transanal mucosectomy to remove the residual at-risk rectal mucosa at the anal transition zone, followed by a hand-sewn ileo-anal pouch anastomosis. However, some studies reported that, even with mucosectomy, some rectal mucosa is left behind. Therefore, a stapled ileal-pouch anal anastomosis is now most commonly performed in this situation and is the recommended approach. Close postoperative endoscopic follow-up is recommended in all patients, whatever surgical procedure is performed. This follow-up usually consists of annual or biannual pouchoscopy (after ileo-anal pouch) or flexible sigmoidoscopy (if the rectum was preserved), and is associated with extra-intestinal surveillance (Ficari et al. 2000).

Recent evidence supports the use of chemoprophylaxis in patients with FAP (Ricciardiello et al. 2016). Aspirin (Ishikawa et al. 2021), sulindac with or without (Giardiello et al. 2002; Samadder et al. 2018), celecoxib (Steinbach et al. 2000) and Omega-3 polyunsaturated fatty acids (West et al. 2010) were shown to reduce the polyp load and/or size in these patients. However, none of these were demonstrated to reduce the incidence of colorectal cancer, and prophylactic surgery therefore remains the gold standard in patients with FAP.

Case 3: Hereditary Non-polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer (HNPCC), also named Lynch syndrome, is a hereditary cancer syndrome associated with germline mutations in the mismatch repair (MMR) genes. Affected genes are mostly MLH1, MSH2, MSH6 or PMS2. The syndrome causes an accumulation of errors during DNA replication, ultimately leading to an increased risk of colorectal cancer, endometrial cancer, ovarian cancer, gastric cancer, small bowel cancer, urinary tract cancer, pancreatic cancer and others (Samadder et al. 2017; Stjepanovic et al. 2019). Patients at risk should undergo regular surveillance and be considered for prophylactic surgery, as both strategies lead to a significant increase in survival.

There are three methods to identify individuals who should be screened for HNPCC: the Amsterdam II criteria, the revised Bethesda criteria and the systematic screening of all colorectal cancer specimens for defective MMR system. First, the Amsterdam II criteria are clinical criteria which identifies individuals at risk for HNPCC (Vasen et al. 1999). The criteria are the following:

- At least three relatives must have a cancer associated with HNPCC
- All of the following criteria should be present:
  One of the relative should be a first-degree relative of the other two
  - At least two successive generations must be affected
  - At least one of the relative with cancer should be diagnosed before the age of 50
  - FAP should be excluded
  - Tumors should be verified whenever possible

In our example, the Amsterdam II criteria were therefore not fulfilled.

Second, the revised Bethesda criteria are usually used by the pathologist to identify operative specimen which should undergo testing for defective MMR mechanism (either by assessing microsatellite stability/instability (MSS/MSI) or by assessing deficient MMR genes) (Umar et al. 2004). The criteria are the following:

Tumors from individuals should be tested for MSI in the following situations:

- Colorectal cancer diagnosed in a patient who is younger than 50 years of age
- Presence of synchronous or metachronous colorectal or other HPNCC-related tumors, regardless of age
- Colorectal cancer with MSI-high histology diagnosed in a patient who is younger than 60 years of age
- Colorectal cancer diagnosed in a patient with one or more first-degree relatives with a HNPCC-related cancer, with one of the cancers being diagnosed below age 50
- Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related cancer regardless of age

However, the Amsterdam II criteria and the revised Bethesda criteria are not 100% sensitive and/or specific to identify patients with HNPCC. In the United Kingdom, these criteria have been replaced by the National Institute for Health and Care Excellence (NICE) guidelines, which recommends screening all preoperative cancer biopsy samples and operative specimens of colorectal cancer for defective MMR system (NIfHaCE 2017). If HNPCC is suspected, tissue samples should be tested either for MSI using PCR and/or for defective MMR-associated proteins using IHC (Li et al. 2020). Considering that approximately 10% of sporadic colorectal cancer cases also display MSI and loss of expression of MLH1 due to hypermethylation of the promoter gene often associated with BRAF V600E mutation, additional analysis for MLH1 hypermethylation and/or BRAF V600E mutation should also be performed in case of defective MLH1. The diagnosis of HNPCC is then confirmed by germline analysis (Stjepanovic et al. 2019).

The management of patients with HPNCC is as follows: 1) surveillance program screening for HPNCC-associated cancers (colonoscopy 1x/1–2 years, transvaginal ultrasound 1x/year, CA-125 tumor marker blood test 1x/year, gastroscopy 1x/1–3 years (Stjepanovic et al. 2019)), 2) offering prophylactic surgery after teenagehood and/or after completion of family (salpingo-oopharectomy, hysterectomy and subtotal colectomy with ileorectal anastomosis versus proctocolectomy and ileo-anal pouch). This strategy should be discussed with the daughter of our patient. Moreover, she should be encouraged to stop smoking and lose weight, if indicated (Stjepanovic et al. 2019). Chemoprophylaxis using Aspirin can also be proposed as it has been shown to reduce the incidence of HNPCC-associated cancers (Burn et al. 2011).

In case of diagnosis of HNPCC after occurrence of cancer, as it is the case in our patient, the ESCP recommendation is to prefer subtotal colectomy with ileorectal anastomosis in patients with mutations in either MLH1 and/or MSH2 considering the increased risk of metachronous colonic cancer. However, this is not the case for rectal cancer, where the surgical resection should not be extended because of the MMR status, except in case of synchronous cancers (Seppala et al. 2021). Moreover, in our example, the patient should have benefited from endometrial cancer screening ideally before, or at least after the surgical procedure. This would have allowed to pick up her endometrial cancer earlier.

The ESMO guidelines recommend administering adjuvant chemotherapy in HNPCC patients with high-risk stage II or stage III colonic cancer. The estimation of the risk was detailed in Question 1 above. Adjuvant chemotherapy does not bring any survival benefit in HNPCC patients with intermediate risk stage II cancer (Kim et al. 2015; Ribic et al. 2003), who generally have better oncological outcomes than their counterparts with sporadic colorectal cancer.

Case 4: Early Rectal Cancer

After endoscopic removal of a malignant polyp, the risk of residual disease depends on several variables, such as the depth of invasion into the submucosa (T1 substages as defined by Kudo (1993), Kikuchi et al. (1995) and Haggitt et al. for pedunculated lesions (Haggitt et al. 1985)), the resection margin (a resection margin <1 mm is considered at higher risk), poor differentiation of the tumor and the presence of lymphovascular invasion (Williams et al. 2013). Using the Kudo-Kikichu classification (Kikuchi et al. 1995;

Kudo 1993), the risk of lymph node metastases was estimated to be 3%, 8% and 23% for cancers involving the higher third (T1sm1), the middle third (T1sm2) and the lower third (T1sm3) of the submucosa (Nascimbeni et al. 2002). Exact definitions of early rectal cancer vary according to variables used to estimate the risk of recurrence (Morino et al. 2015), but it is commonly admitted that rectal cancer at lowest risk of recurrence (T1 sm1, no lymphovascular invasion, good differenciation) can be considered as early rectal cancer. For these cancers, local excision constitutes a valid treatment option (Morino et al. 2015) and an alternative to the more morbid anterior resection with total mesorectal excision, which constitutes the standard of care for more locally advanced rectal cancers. Moreover, a diameter criteria (4 cm, <30% of circumferential rectal wall) is usually considered for technical reasons (Morino et al. 2015).

In our example, the mid rectal polyp was initially staged as being high-grade dysplasia, without any evidence of adenocarcinoma. However, the lesion was described as being flat (Paris 0-IIa) with a depressed centre, and therefore potential malignancy had to be considered. Therefore, a standard polypectomy was not performed. However, an endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) could have been performed by an experienced gastroenterologist in the absence of a depressed centre.

In our scenario, a pelvic MRI was performed to better characterize the lesion, which was then defined as mrT1/2 V0 N0 M0. Of note, the TREND study comparing EMR versus transanal endoscopic microsurgery (TEM) for resection of non-cancerous polyps showed that 13% of lesions preoperatively staged as benign tumors turned out to be malignant (Barendse et al. 2018). There is also an ongoing randomized controlled trial (TRIASSIC trial) comparing transanal minimally invasive surgery (TAMIS) versus ESD, with results are awaited (Dekkers et al. 2020). An endoanal ultrasound would have allowed to better define the T stage, but was unfortunately not available. The patient underwent transanal minimally invasive surgery (TAMIS) with full-thickness dissection. TAMIS can be either performed using the TEM system or using more recent transanal plateforms, such as the GelPoint (Rimonda et al. 2013). Transanal surgery performed without TAMIS should be reserved to very distal tumors due to the suboptimal exposure increasing the risk of R1/R2 resection (Morino et al. 2015). TAMIS dissection can be either simple mucosectomy or full-thickness excision, which allows collection of a better specimen for the pathologist and potentially reaching better surgical margins. In our example, pathology showed a pT1sm1 L0 V0 R0 adenocarcinoma, which is at low risk of local recurrence. Therefore, the patient can enter a surveillance program and does not need more extended resection or any adjuvant therapy.

Case 5: Non-metastatic Rectal Cancer

Rectal cancer is most commonly defined as a cancer within 15 cm from the anal verge (Glynne-Jones et al. 2017). From an anatomical perspective, rectal cancer can be defined as a cancer affecting "*the portion of the large bowel below the sacral promontory that is surrounded by a definable mesorectum posteriorly*" (Beyond TMEC 2013). Rectal cancer is usually subdivided into high rectal cancer (10–15 cm from the anal verge), mid rectal cancer (5–10 cm from the anal verge) and low rectal cancer (<5 cm from the anal verge) (Glynne-Jones et al. 2017). Other definitions, which are more useful in determining the best surgical strategy can be used, such as the LOREC definition for low rectal cancer (Moran et al. 2014). The localization of the cancer can be accurately evaluated by rigid rectoscopy and/or pelvic MRI.

Historically, Heald et al. introduced in 1989 the concept of total mesorectal excision (TME), which involves completely removing an intact mesorectum *en bloc* with the rectum itself (Heald and Ryall 1986). This concept led to an important decrease in the incidence of local recurrence and in improved survival. For a mid-rectal cancer, as is the case in our scenario, the recommendation is to perform a complete TME down to the pelvic floor, in order to remove para-rectal draining lymph nodes, associated with a proximal ligation of the inferior mesenteric artery (Glynne-Jones et al. 2017; Moran et al. 2017). This ligation can be "high tie" (1–2 cm distal to the aorta – which corresponds to a D3 lymphadenectomy) or "low tie" (after the division of the ascending left colic artery – which corresponds to a D2 lymphadenectomy) (Hajibandeh et al. 2020). The recommended distal margin on the rectum itself (and not on the TME) is usually considered to be at least 1 cm, but the true requirement is the possibility to be able to apply a stapling device or to divide the distal rectum without disrupting the tumor (Karanjia et al. 1990; Williams et al. 1983). In case this is not feasible, the tumor is considered as being a low rectal cancer. The LOREC defines such cancer as "*an adenocarcinoma with its lower edge at, or below, the origin of the levators on the pelvic side-wall*" (Moran et al. 2014), and in this case an abdomino-perineal excision of the rectum (APER) may well be required.

Locally advanced primary rectal cancer is defined as a rectal cancer extending beyond the TME plane and that requires *an extended surgical resection beyond the TME plane to achieve a pathological R0 resection* (Beyond TMEC 2013). In our scenario, the mesorectal fascia was defined as being threatened on the staging pelvic MRI (also indicated as threatened circumferential resection margin (CRM+)). This is defined as a tumor and/or a lymph node located ≤1 mm from the mesorectal fascia (Group MS 2006). Considering this threatened CRM, the ESMO recommends pre-operative chemoradiotherapy (conventional scheme or, alternatively, short-course radiotherapy combined with FOLFOX chemotherapy and long-wait) followed by TME (or beyond TME resection in this case).

As for the surgical approach for colon cancer, the recommended surgical approach is via laparoscopy (Moran et al. 2017; NIfHaCE 2020). Two randomized controlled trials have supported this strategy and established that laparoscopy has better short-term outcomes than open surgery with similar oncological outcomes (Bonjer et al. 2015; van der Pas et al. 2013). Two other randomized controlled trials have failed to demonstrate non-inferiority of laparoscopic rectal surgery when compared to open rectal surgery in terms of cancer clearance/pathological outcomes (Fleshman et al. 2015; Stevenson et al. 2015), but showed similar oncological outcomes (Fleshman et al. 2019; Stevenson et al. 2019). It should be noted that the conversion rate from laparoscopy to open surgery was approximately 10% (Fleshman et al. 2015; Stevenson et al. 2015). Indeed, laparoscopic TME is particularly challenging in male patients, who have a narrower pelvis, especially in the presence of morbid obesity. Therefore, several alternative minimally invasive approaches allowing TME in these patients have been developed, such as transanal TME (taTME) and robotic TME. However, the ROLARR trial did not show any significant difference between laparoscopic TME and robotic TME in terms of quality of surgical resection and conversion to open in the treatment of rectal cancer (Jayne et al. 2017). Moreover, a network meta-analysis of randomized controlled trials did not show any important differences between the techniques (Simillis et al. 2019). At present, whilst a minimally invasive technique is generally preferable, it is important that the mode of access is not the most important factor and that appropriate rectal cancer surgery is performed irrespective of access, to facilitate clear resection margins whilst aiming for potential cure.

Finally, to conclude this scenario, if the patient had complete clinical response (CCR) after neoadjuvant treatment, organ preservation and entering a "watch and wait" surveillance program could constitute an option. This approach was popularized by Habr-Gama in 2004 (Habr-Gama et al. 2004) and has been supported by encouraging reports (Smith et al. 2019; van der Valk et al. 2018). However, as CCR does not correspond to compete pathological response, these patients are at risk of local recurrence and should be closely followed-up with regular digital rectal examination, MRI and flexible endoscopy. Moreover, this approach should be reserved for the moment to selected cases with good compliance, and with shared patient decision making.

Case 6: Lateral Pelvic Lymph Nodes

This scenario depicts the case of a locally advanced rectal cancer which will require beyond TME resection using an extralevator abdominoperineal excision (ELAPE) in order to achieve an R0 resection (Beyond TMEC 2013; Moran et al. 2017). However, this tumor did not only extend locally but also likely metastasized into the lateral pelvic sidewall lymph nodes, which may expose the patient to an important risk of recurrence (Kim et al. 2008). These nodes include the internal iliac nodes, common iliac nodes, obturator nodes, and external iliac nodes (Bell et al. 2009). The prevalence of lateral pelvic sidewall lymph node metastasis in patients with mid/low rectal cancer is estimated to be around 17.3% (Christou et al. 2021) and is inversely proportional to tumor height from the anal verge (Ueno et al. 2005). In Western countries, suspected involvement of these lymph nodes will constitute an indication for chemoradiotherapy with or without a radiotherapy boost (Glynne-Jones et al. 2017). In case of absence or partial response after neoadjuvant treatment, the therapeutic strategy varies between observation or surgery in the form of lateral lymph node dissection (Hazen et al. 2021). Restaging MRI should be performed as it allows identification of lymph nodes at higher risk of recurrence (those with no shrinkage of lymph node diameter and/or with post-treatment lymph node ≥0.5 cm) (Malakorn et al. 2019; Ogura et al. 2019). In Asia, lateral lymph node dissection is the preferred approach and can be performed unilaterally or bilaterally (Kanemitsu et al. 2017). Ongoing controversy exists regarding treatments for suspicious lateral pelvic side wall lymph nodes and indications for lateral lymph node dissection. Some authors recommend performing a selective approach, with excision being performed either via open or minimally invasive (laparoscopic or robotic) surgery (Kim et al. 2020).

References

Andre, T., Boni, C., Mounedji-Boudiaf, L. et al. (2004). Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350: 2343–2351.

Argiles, G., Tabernero, J., Labianca, R. et al. (2020). Localised colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 31: 1291–1305.

Barendse, R.M., Musters, G.D., Ejr, D.G. et al. (2018). Randomised controlled trial of transanal endoscopic microsurgery versus endoscopic mucosal resection for large rectal adenomas (TREND Study). *Gut* 67: 837–846.

Bastiaenen, V.P., Hovdenak Jakobsen, I., Labianca, R. et al. (2019). Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology. *Colorectal Dis* 21: 392–416.

Bell, S., Sasaki, J., Sinclair, G. et al. (2009). Understanding the anatomy of lymphatic drainage and the use of blue-dye mapping to determine the extent of lymphadenectomy in rectal cancer surgery: unresolved issues. *Colorectal Dis* 11: 443–449.

Beyond TMEC. (2013). Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg* 100: 1009–1014.

Bonjer, H.J., Deijen, C.L., Abis, G.A. et al. (2015). A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 372: 1324–1332.

Burn, J., Gerdes, A.M., Macrae, F. et al. (2011). Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 378: 2081–2087.

Christou, N., Meyer, J., Combescure, C. et al. (2021). Prevalence of metastatic lateral lymph nodes in Asian patients with lateral lymph node dissection for rectal cancer: a meta-analysis. *World J Surg* 45: 1537–1547.

Dekkers, N., Boonstra, J.J., Moons, L.M.G. et al. (2020). Transanal minimally invasive surgery (TAMIS) versus endoscopic submucosal dissection (ESD) for resection of non-pedunculated rectal lesions (TRIASSIC study): study protocol of a European multicenter randomised controlled trial. *BMC Gastroenterol* 20: 225.

Ficari, F., Cama, A., Valanzano, R. et al. (2000). APC gene mutations and colorectal adenomatosis in familial adenomatous polyposis. *Br J Cancer* 82: 348–353.

Fleshman, J., Branda, M., Sargent, D.J. et al. (2015). Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. *JAMA* 314: 1346–1355.

Fleshman, J., Branda, M.E., Sargent, D.J. et al. (2019). Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Ann Surg* 269: 589–595.

Giardiello, F.M., Yang, V.W., Hylind, L.M. et al. (2002). Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 346: 1054–1059.

Grothey, A., Sobrero, A.F., Shields, A.F. et al. (2018). Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 378: 1177–1188.

Group MS. (2006). Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 333: 779.

Gustafsson, U.O., Scott, M.J., Hubner, M. et al. (2019). Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS((R))) society recommendations: 2018. *World J Surg* 43: 659–695.

Habr-Gama, A., Perez, R.O., Nadalin, W. et al. (2004). Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 240: 711–717; discussion 717-8.

Haggitt, R.C., Glotzbach, R.E., Soffer, E.E. et al. (1985). Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 89: 328–336.

Hajibandeh, S., Hajibandeh, S., and Maw, A. (2020). Meta-analysis and trial sequential analysis of randomized controlled trials comparing high and low ligation of the inferior mesenteric artery in rectal cancer surgery. *Dis Colon Rectum* 63: 988–999.

Hazen, S.M., Sluckin, T., Beets, G. et al. (2021). Current practices concerning the assessment and treatment of lateral lymph nodes in low rectal cancer: a survey among colorectal surgeons in The Netherlands. *Acta Chir Belg* 1–9.

Heald, R.J. and Ryall, R.D. (1986). Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1: 1479–1482.

Hohenberger, W., Weber, K., Matzel, K. et al. (2009). Standardized surgery for colonic cancer: complete mesocolic excision and central ligation–technical notes and outcome. *Colorectal Dis* 11: 354–364; discussion 364-5.

Ishikawa, H., Mutoh, M., Sato, Y. et al. (2021). Chemoprevention with low-dose aspirin, mesalazine, or both in patients with familial adenomatous polyposis without previous colectomy (J-FAPP Study IV): a multicentre, double-blind, randomised, two-by-two factorial design trial. *Lancet Gastroenterol Hepatol* 6: 474–481.

Jayne, D., Pigazzi, A., Marshall, H. et al. (2017). Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. *JAMA* 318: 1569–1580.

Jayne, D.G., Guillou, P.J., Thorpe, H. et al. (2007). Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 25: 3061–3068.

Kanemitsu, Y., Komori, K., Shida, D. et al. (2017). Potential impact of lateral lymph node dissection (LLND) for low rectal cancer on prognoses and local control: a comparison of 2 high-volume centers in Japan that employ different policies concerning LLND. *Surgery* 162: 303–314.

Karanjia, N.D., Schache, D.J., North, W.R. et al. (1990). 'Close shave' in anterior resection. *Br J Surg* 77: 510–512.

Kennedy, R.H., Francis, E.A., Wharton, R. et al. (2014). Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: enROL. *J Clin Oncol* 32: 1804–1811.

Kikuchi, R., Takano, M., Takagi, K. et al. (1995). Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum* 38: 1286–1295.

Kim, J.E., Hong, Y.S., Kim, H.J. et al. (2015). Defective mismatch repair status was not associated with DFS and OS in stage II colon cancer treated with adjuvant chemotherapy. *Ann Surg Oncol* 22 (Suppl 3): S630–7.

Kim, M.J., Chang, G.J., Lim, H.K. et al. (2020). Oncological impact of lateral lymph node dissection after preoperative chemoradiotherapy in patients with rectal cancer. *Ann Surg Oncol* 27: 3525–3533.

Kim, T.H., Jeong, S.Y., Choi, D.H. et al. (2008). Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 15: 729–737.

Kudo, S. (1993). Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy* 25: 455–461.

Li, K., Luo, H., Huang, L. et al. (2020). Microsatellite instability: a review of what the oncologist should know. *Cancer Cell Int* 20: 16.

Malakorn, S., Yang, Y., Bednarski, B.K. et al. (2019). Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? *Dis Colon Rectum* 62: 1158–1166.

Moran, B., Cunningham, C., Singh, T. et al. (2017). Association of coloproctology of Great Britain & Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017) - surgical management. *Colorectal Dis* 19 (Suppl 1): 18–36.

Moran, B.J., Holm, T., Brannagan, G. et al. (2014). The English national low rectal cancer development programme: key messages and future perspectives. *Colorectal Dis* 16: 173–178.

Morino, M., Risio, M., Bach, S. et al. (2015). Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. *Surg Endosc* 29: 755–773.

Nascimbeni, R., Burgart, L.J., Nivatvongs, S. et al. (2002). Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 45: 200–206.

NIfHaCE (NICE). (2017). Molecular testing strategies for Lynch syndrome in people with colorectal cancer. Volume Diagnostics guidance [DG27].

NIfHaCE (NICE). (2020). Colorectal cancer: NICE guideline (NG151).

Ogura, A., Konishi, T., Beets, G.L. et al. (2019). Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. *JAMA Surg* 154: e192172.

Ribic, C.M., Sargent, D.J., Moore, M.J. et al. (2003). Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 349: 247–257.

Ricciardiello, L., Ahnen, D.J., and Lynch, P.M. (2016). Chemoprevention of hereditary colon cancers: time for new strategies. *Nat Rev Gastroenterol Hepatol* 13: 352–361.

Rimonda, R., Arezzo, A., Arolfo, S. et al. (2013). TransAnal Minimally Invasive Surgery (TAMIS) with SILS port versus Transanal Endoscopic Microsurgery (TEM): a comparative experimental study. *Surg Endosc* 27: 3762–3768.

Rutter, M.D., East, J., Rees, C.J. et al. (2020). British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 69: 201–223.

Samadder, N.J., Kuwada, S.K., Boucher, K.M. et al. (2018). Association of sulindac and erlotinib vs placebo with colorectal neoplasia in familial adenomatous polyposis: secondary analysis of a randomized clinical trial. *JAMA Oncol* 4: 671–677.

Samadder, N.J., Smith, K.R., Wong, J. et al. (2017). Cancer risk in families fulfilling the Amsterdam criteria for Lynch syndrome. *JAMA Oncol* 3: 1697–1701.

Seppala, T.T., Latchford, A., Negoi, I. et al. (2021). European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. *Br J Surg* 108: 484–498.

Simillis, C., Lal, N., Thoukididou, S.N. et al. (2019). Open versus laparoscopic versus robotic versus transanal mesorectal excision for rectal cancer: a systematic review and network meta-analysis. *Ann Surg* 270: 59–68.

Smith, J.J., Strombom, P., Chow, O.S. et al. (2019). Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol* 5: e185896.

Steinbach, G., Lynch, P.M., Phillips, R.K. et al. (2000). The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 342: 1946–1952.

Stevenson, A.R., Solomon, M.J., Lumley, J.W. et al. (2015). Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *JAMA* 314: 1356–1363.

Stevenson, A.R.L., Solomon, M.J., Brown, C.S.B. et al. (2019). Disease-free survival and local recurrence after laparoscopic-assisted resection or open resection for rectal cancer: the Australasian laparoscopic cancer of the rectum randomized clinical trial. *Ann Surg* 269: 596–602.

Stjepanovic, N., Moreira, L., Carneiro, F. et al. (2019). Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. *Ann Oncol* 30: 1558–1571.

Ueno, M., Oya, M., Azekura, K. et al. (2005). Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. *Br J Surg* 92: 756–763.

Umar, A., Boland, C.R., Terdiman, J.P. et al. (2004). Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 96: 261–268.

van der Pas, M.H., Haglind, E., Cuesta, M.A. et al. (2013). Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 14: 210–218.

van der Valk, M.J.M., Hilling, D.E., Bastiaannet, E. et al. (2018). Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 391: 2537–2545.

Vasen, H.F., Watson, P., Mecklin, J.P. et al. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 116: 1453–1456.

West, N.J., Clark, S.K., Phillips, R.K. et al. (2010). Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 59: 918–925.

Williams, J.G., Pullan, R.D., Hill, J. et al. (2013). Management of the malignant colorectal polyp: ACPGBI position statement. *Colorectal Dis* 15 (Suppl 2): 1–38.

Williams, N.S., Dixon, M.F., and Johnston, D. (1983). Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival. *Br J Surg* 70: 150–154.

Xu, L., Su, X., He, Z. et al. (2021). Short-term outcomes of complete mesocolic excision versus D2 dissection in patients undergoing laparoscopic colectomy for right colon cancer (RELARC): a randomised, controlled, phase 3, superiority trial. *Lancet Oncol* 22: 391–401.

Yothers, G., O'Connell, M.J., Allegra, C.J. et al. (2011). Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 29: 3768–3774.

13 Epidemiology, Pathology, Diagnosis, Prevention, and Management of Anal Cancer

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[Aspects of stoma management are cover in Chapter 12].

Introduction

Anal cancer is considered a relatively uncommon malignancy and accounts for 3–4% of gastrointestinal tract cancers, with an estimated incidence rate of 0.54 per 100,000. The estimated number of worldwide new cases of anal cancer in 2020 was 50,865, with 19,293 deaths related to anal cancer in the same year. More patients were diagnosed in women with a female-to-male ratio of 3:2 (GLOBOCAN 2020). The incidence of anal cancer has also increased in recent years, especially in high-income countries. Infection with high-risk subtypes of human papillomaviruses (HPV), untreated human immunodeficiency virus (HIV), men who have sex with men, and females with a history of HPV-induced cervical, vaginal or vulvar cancer, and those who are immunocompromised are at higher risk of developing anal cancer (Wieland and Kreuter 2019).

The current standard treatment for anal cancer is synchronous chemoradiotherapy (CRT). Surgical resection in the form of abdominoperineal resection (APR) of the anal canal and rectum with the formation of a permanent colostomy is reserved for residual or recurrent disease after primary CRT. Overall, survival from anal cancer now approaches 80% at five years.

While we may see more cases of anal cancer in the short-term future, this may be ultimately balanced by preventative measures including HPV vaccination, more accurate characterization and treatment of early *(in situ)* disease, and the optimization of chemoradiation regimens.

Aetiology

- Risk factors

Human papillomavirus (HPV) infection is considered the most important etiologic agent for anal cancer. Similar to cervical intraepithelial neoplasia, HPV can cause anal intraepithelial neoplasia (AIN). This may progress to invasive cancer through a complex interplay between HPV infection and subsequent DNA integration and stepwise mutations in tumor suppressor genes (Gervaz et al. 2006). While HPV is the likely causative agent of anal cancer, the immune status may determine the time of progression to anal cancer.

While anal cancer is rare in the general population, the incidence rates of anal cancer are higher in some individual groups. In a meta-analysis of anal cancer incidence by risk groups, HIV-positive men who have sex with men (MSM) had the highest incidence rate of anal cancer (85 per 100,000 person-years [py]). This was followed by non-MSM male persons living with HIV (PLHIV) (35 per 100,000 py) and female PLHIV (22 per 100,000 py). A substantial variation by age was also noticed in these groups (from 16.8 to 107.5 in < 30 years and ≥60 years HIV-positive MSM, respectively). The incidence rates for anal cancer were also much higher after diagnosis of vulvar than cervical or vaginal cancer (48 versus 9 and 10 per 100,000 py). The incidence rate was 13 in solid organ transplant recipients, with the risk increasing as the duration of the transplant increases, reaching 24.5 and 49.6 for males and females >10 years after transplant. Patients with autoimmune diseases such as systemic lupus erythematosus, ulcerative colitis, and Crohn's disease were also reported to have a slightly increased incidence rate of anal cancer (10, 6, and 3 per 100,000 py, respectively) (Clifford et al. 2021).

A unifying anal cancer risk scale was developed based on the incidence rates of anal cancer among populations considered at significantly higher risk (Figure 1). The scale represents the broad spectrum of anal cancer burden among the different populations and identifies high-risk groups in whom anal cancer screening and secondary prevention.

- Pathology

Squamous tumors of the cutaneous anal margin, defined as the circumferential area of pigmented skin lying outside the anal verge extending laterally to a radius of 5 cm, can be treated

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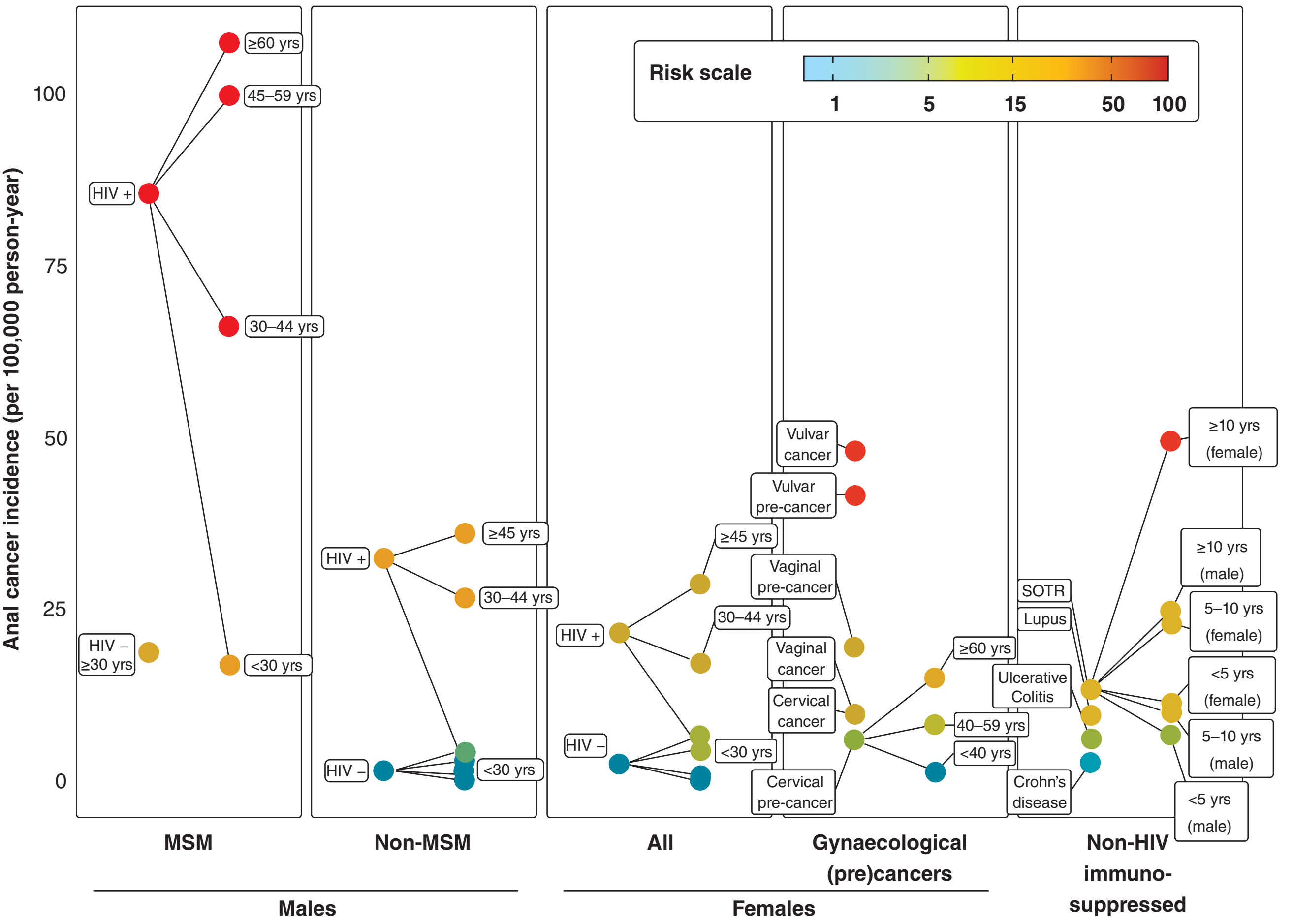

Figure 1 Anal cancer risk scale. (Clifford et al. 2021/with permission of John Wiley & Sons).

like skin lesions with wide excision, which can result in 80% five-year survival. True anal canal cancer arises from the squamous epithelium lining the distal anal canal, which changes to a transitional epithelium near the dentate line and ultimately to the non-squamous rectal mucosa. Distal anal tumors tend to have a keratinizing squamous morphology. In contrast, more proximal tumors are less likely to be keratinized (cloacogenic or basaloid) (Williams and Talbot 1994), yet this distinction is of little clinical relevance. Rare anal canal tumors include adenocarcinomas of the anal ducts or glands (which behave almost identically to rectal adenocarcinoma) and anal melanoma.

Anal cancer typically spreads initially through the lymphatic system. Inguinal and femoral lymph nodes are more frequently affected below the dentate line, whereas the proximal anal canal drains to perirectal nodes. About 10% of individuals initially exhibit synchronous groin nodal illness. In 10–20% of patients receiving treatment for anal cancer, distant metastases (often to the liver and lungs) manifest.

- Screening and prevention

There is an increased risk of malignant transformation for some HPV subtypes. Immunization against HPV type 16 has been shown to reduce the incidence of cervical neoplasms, and several nations are exploring making this practice more widely available. Additionally, this might help prevent the development of anal cancer. Smoking is likely to raise the risk of anal cancer.

Anatomy

- The anal canal, anal verge, and anal margin

The anal canal starts at the anorectal junction at the level of the puborectalis sling and extends to the anal verge, which coincides with the inter-sphincteric groove. The anal margin is the circumferential area of pigmented skin lying outside the anal verge extending laterally to a radius of 5 cm. Cancers of the anal margin are considered anal cancers, while cancers outside the anal margin are classified as skin cancers. The columnar epithelium of the rectum extends to cover the upper part of the anal canal above the anal transition zone, which lies about 1 cm above the dentate line. The anal canal distal to the dentate line is covered by squamous epithelium.

- Lymphatic drainage

The lymphatic drainage of the proximal anal canal follows the rectal lymphatic drainage to perirectal paravertebral lymph nodes. In contrast, the area just proximal to the dentate line drains into the internal pudendal and internal iliac lymphatics, while the anal canal below the dentate line and the anal margin is drained by the inguinal, femoral, and external iliac lymph nodes.

Diagnosis

- Symptoms

Anal cancer symptoms are often nonspecific, with the most typical symptom being fresh rectal bleeding. This is often misattributed to other benign anal conditions such as hemorrhoids leading to the often-delayed diagnosis of anal cancer. Anal cancer may also present as anal pain, itching, discharge, mass, non-healing ulcer, and incontinence. Perianal pain, painful defecation, and weight loss are common features of advanced (T3/T4) disease (Sauter et al. 2016). Rarely may patients present with enlarged inguinal lymph nodes, and a minority of patients are asymptomatic. The patient assessment also includes discussing sexual activity, previous history of sexually transmitted diseases, and the risk of immunosuppression.

- Examination and clinical findings

Digital rectal examination (DRE) is essential in assessing anal cancer. A mass is usually identified. The size and position of the mass and fixity to the surrounding structure should be evaluated and documented. Enlarged perirectal lymph nodes are evident on digital examination of the rectum in some patients. A gynecological exam is performed in women to assess if vaginal involvement or a fistula is present. Synchronous vulvar, vaginal or cervical neoplasia may coexist. Draining nodal basins are checked, and a general examination for distant metastases is performed.

When a clinically suspicious lesion is found, a diagnosis of anal cancer depends on cytologic or histologic confirmation. Examination under anesthesia provides an optimum assessment of the tumor and involvement of nearby structures and facilitates biopsy to confirm the diagnosis. Appropriate biopsies with accompanying clinical information should allow the pathologist to diagnose anal cancer confidently.

- Staging and other investigations MRI, CT CAP, PET CT

The TNM (tumor-node-metastasis) staging system is based on tumor size and nodal status (Tables 1 & 2) (Brierley et al. 2017) The Tumor (T) staging depends on the tumor size and invasion of adjacent organs. This can be assessed by clinical examination; however, magnetic resonance imaging (MRI) is considered the mainstay of local staging and provides a more detailed assessment of the tumor extent.

Endoanal ultrasound scan is highly sensitive in detecting anal cancer and can detect up to 100% of cases and is superior to MRI scans for T1 tumors (Tumor size less than 2 cm) (Sauter et al. 2016); however, it is user-dependent and less sensitive for nodal involvement.

The MRI scanning techniques for anal cancer are similar to rectal cancer and consist of 3 T2-weighted sequences in sagittal, axial, and coronal planes, which are angled perpendicular or parallel to the anal canal. A T1-weighted sequence covering the whole pelvis is required to image nodal disease. The tumor will have a relatively high signal intensity compared to the low signal intensity of the surrounding muscle (Maas et al. 2020) MRI has the advantage of multiplanar visualization. It is less user-dependent than endoanal ultrasound. Many clinicians find the ability to project and compare images (especially follow-up images in questions of recurrence) in a multidisciplinary review extremely useful.

The MRI report should include the relationship of the lower edge of the tumor to the anal margin, the tumor extent with quadrant involvement of the anal canal or rectum, the craniocaudal tumor length, and its depth of invasion. Any evidence of adjacent organ infiltration such as vagina, prostate, urethra, or bladder wall should also be reported. The MRI scan should also report on draining lymph nodes sites and should include both inguinal regions, the pelvic sidewalls, and the top of the mesorectum up to the L5 level (Rao et al. 2021).

CT of the pelvis is often obtained during staging for distant disease. Still, as for rectal cancer, it does not reveal the layers of the anorectal region nor differentiate between tumor and normal pelvic tissues as clearly as MRI.

- LN

Unlike rectal cancer, the nodal (N) staging of anal cancer depends on the site rather than the number of involved lymph nodes (Table 1). The presence of nodal disease has important implications for prognosis and may require alterations in treatment. Involvement of perirectal lymph nodes may be more frequent but are clinically less important as such nodes are included in the radiotherapy fields of the primary tumor. In

Table 1 UICC TNM (8th edition) clinical classification for anal cancer.

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Bowen disease, HSIL, AIN II-III)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumors more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder (direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4)
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
N1a	Metastases in inguinal, mesorectal, and/or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastases in external iliac and in inguinal, mesorectal and/or internal iliac lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

AIN, anal intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; TNM, tumor–node–metastasis; UICC, Union for International Cancer Control (Brierley et al. 2017).

Table 2 UICC pTNM (8th edition) stage classification of anal cancer.

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-T2	N1	M0
Stage IIIB	T4	N0	M0
Stage IIIC	T3-T4	N1	M0
Stage IV	Any T	Any N	M1

TNM, tumor node metastasis; UICC, Union for International Cancer Control (Brierley et al. 2017).

contrast, the diagnosis of involved inguinal or iliac nodes may demand additional radiation to these fields.

MRI features that will suggest lymph node involvement include enlargement of the lymph node (largest short-axis diameter > 1 cm for mesorectal nodes and > 1.5 cm for other nodes), heterogeneity, necrosis, irregular contours, and strong enhancement. However, these radiological criteria for lymph node metastasis have not been validated due to the scarcity of surgical specimens (Durot et al. 2017).

It is technically possible to perform a sentinel lymph node biopsy utilizing lymphoscintigraphy with patent blue dye injected near the tumor site. The presence of microscopic disease can then be examined in this sentinel node. Tumors involving the midline of the anal canal commonly spread to both inguinal lymphatic basins. It has been suggested that patients without inguinal node involvement may be able to avoid the risks of prophylactic inguinal irradiation thanks to sentinel lymph node biopsy. Around 20% of patients were found to have subclinical lymph node disease at sentinel node biopsy in some reported studies (Damin et al. 2006).

- PET CT

The majority (90%) of anal cancers are avid on positron emission tomography (PET) CT with 18-fluorodeoxyglucose (FDG–PET-CT). The metanalysis by Mahmud et al. on the role of PET scan in anal cancer recommended that (FDG–PET-CT) adds value to conventional imaging in the initial staging of T2-T4 anal cancer with a change in the treatment plan; mainly in the term of radiotherapy dosage or field changes, in a significant number of patients (12.5–59.3%) to justify the routine use of PET-CT in the staging of locally advanced anal cancer (Mahmud et al. 2017). While achieving a complete response to treatment on PET-CT is a good prognostic factor for overall and progression-free survival, insufficient evidence was found to recommend routine PET-CT in assessing treatment response (Mahmud et al. 2017).

PET-CT is beneficial in cases with enlarged lymph nodes which lack other radiological features of disease involvement.

Around 50% of enlarged inguinal lymph nodes in patients with anal cancer are reactionary lymph nodes. Further characterization of these lymph nodes through an ultrasound-guided fine-needle aspiration (FNA) is recommended when radiological features of disease involvement are absent on MRI and PET-CT to avoid morbidity from irradiation of the inguinal regions (Rao et al. 2021).

- Distant spread

Hematogenous spread of anal cancer typically affects the liver and lungs. The imaging modalities most frequently utilized to identify metastases to these areas are contrast-enhanced CT and MRI. CT scans of the chest, abdomen, and pelvis are generally used for the staging of distant disease, and MRI for local staging due to cost and time efficiency.

Figure 2 summaries a diagnostic algorithm for anal cancer as recommended by the European society of medical oncology (ESMO) (Rao et al. 2021).

Treatment

- CRT

The main aim of anal cancer treatment is to cure locoregional disease while preserving anal function and quality of life. Since Nigro's 1974 publication (Nigro et al. 1974) of pathologic complete responses in two of three anal cancer patients following low-dose radiotherapy and synchronous mitomycin C (MMC) and 5-fluorouracil (5-FU) given before abdominoperineal resection, numerous additional studies (Table 3) have established that primary CRT is suitable for the majority of patients, with the significant benefit of preserved anal sphincter function without an apparent adverse effect on overall survival. The treatment protocol used by Nigro was a combination of radiotherapy as 3000 rad (30 Gy) over three weeks (200 rad per day, 5 days a week) with a combination of Chemotherapy in the form of 5-fluorouracil infusion (1g/m2 on days 1–4 and repeated on days 29–32) and a single dose of Mitomycin C intravenous bolus (15 mg/m2) on day 1. Surgery was done at 4–6 weeks intervals from the end of radiation therapy (Nigro et al. 1983). About 80% of anal cancer patients will be treated initially with CRT.

Two studies in the 1980s compared the outcomes of CRT with those of historical controls who had only had radiotherapy, pointing to enhanced local control with the addition of chemotherapy (Cummings 1984; Papillon and Montbarbon 1987). Two randomized trials later supported these results in the 1990s, the EORTC and UKCCCR ACT I study, concluding the superiority of combined CRT with 5-FU and MMC over radiotherapy alone (Bartelink et al. 1997; Northover et al. 1996). In 1996, The RTOG 87–04 study compared the radiotherapy combination with 5FU alone against the combination of 5FU and MMC and reported the superiority of the combined effect of 5FU and MMC (Flam et al. 2016).

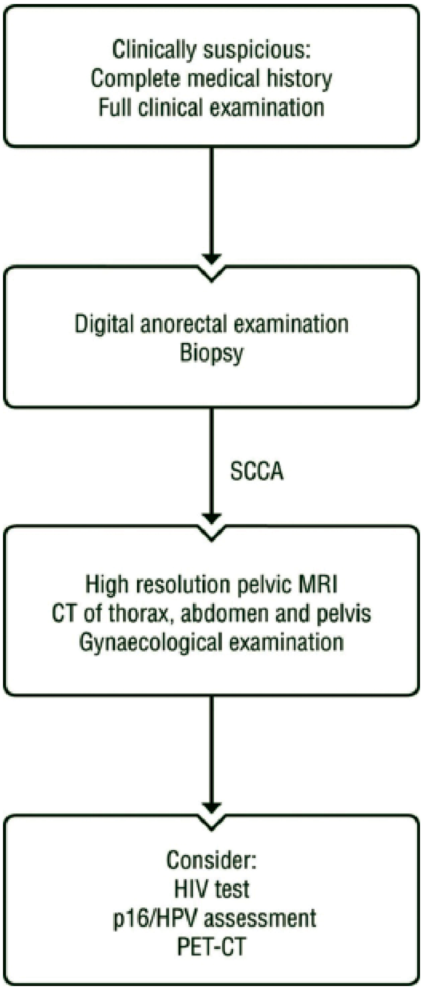
Clinically suspicious:
Complete medical history
Full clinical examination
Digital anorectal examination
Biopsy
SCCA
High resolution pelvic MRI
CT of thorax, abdomen and pelvis
Gynaecological examination
Consider:
HIV test
p16/HPV assessment
PET-CT

Figure 2 Diagnostic algorithm for anal cancer.

CT, computed tomography; HIV, human immunodeficiency virus; HPV, human papillomavirus; MRI, magnetic resonance imaging; PET, positron emission tomography; SCCA, squamous-cell carcinoma of the anus (Rao et al. 2021/with permission of Elsevier).

The next cohort of clinical trials focused on comparing cisplatin (CisP) against MMC in combination with 5FU and radiotherapy in treating SCC of the anal canal. The RTOG 98 –11 (Ajani et al. 2008) and CRUK ACT II (James et al. 2013) trials concluded that cisplatin did not improve outcomes, including complete response rate and DFS, when compared with MMC. The UNICANCER ACCORD 03 trial examined whether a greater radiation boost or two cycles of induction chemotherapy before concurrent RCT may improve colostomy-free survival. The study reported that neither induction

Table 3 Randomized studies of the treatment of anal cancer.

Study and design	No. of patients	Local failure	Colostomy-free survival	Disease-free survival	Overall survival
UKCCCR (Northover et al. 1996)	585				
5FU/RT		59%		61%	58%
5FU/MMC/RT		36%		72%	65%
		P = <0.0001			p = 0.25
EORTC (Bartelink et al. 1997)	110				
RT		50%	40%		52%
5FU/MMC/RT		40%	73%		59%
		p = 0.02	p = 0.002		NS
ECOG/RTOG (Flam et al. 2016)	310				
5FU/RT			59%	51%	42%
5FU/MMC/RT			71%	73%	32%
			p = 0.014	p = 0.0003	NS
RTOG 98–11 (Ajani et al. 2008)	644				
Two cycles CisP/5FU then MMC/5FU/RT			72%	68%	78%
Two cycles CisP/5FU then CisP/5FU/RT			65%	58%	70%
			p = 0.05	p = 0.006	p = 0.026
CRUK ACT II (James et al. 2013)	940				
5FU/MMC/RT			68%	69%	79%
5FU/CisP/RT			67%	69%	77%
			NS	NS	NS
No maintenance			66%	69%	79%
Maintenance (5FU/CisP)			69%	70%	76%
			NS	NS	NS
ACCORD 03 (Peiffert et al. 2012)	307				
Neoadjuvant 5FU/CisP + 5FU/CisP/RT + LD booster RT			67%	70%	74.5%
Neoadjuvant 5FU/CisP + 5FU/CisP/RT + HD booster RT			82%	78%	
5FU/CisP/RT + LD booster RT			77%	67%	71%
5FU/CisP/RT + HD booster RT			72%	68%	

RT = radiotherapy, 5FU=5Fluorouracil, CisP=Cisplatinum, MMC=Mitomycin C, NS= not significant, HD=high-dose, LD=low-dose. All p-values relate to Hazard Ratios.

chemotherapy nor higher boost radiotherapy improved outcomes (Peiffert et al. 2012).

The commonly used dose of 5-FU is 1gm/m^2 on days 1–4, and 29–32 of radiotherapy and MMC is either given as 12 mg/m^2 on days 1 (James et al. 2013) or 10 mg/m^2 on days 1 and 29 (Ajani et al. 2008) Recently, 5FU has been replaced with oral capecitabine (825 mg/m2 twice daily for five days per week) for all days of radiotherapy (Glynne-Jones et al. 2008).

There is no consensus on the optimal curative radiotherapy dose for anal cancer, and treatment protocols vary from 45 to 60 Gy, including the boost doses. The radiotherapy dose for locally advanced anal cancer should be more than 50.4 Gy (James et al. 2013). The initial treatment field should include the primary tumor, the anal canal, and nodal regions, including the inguinal canal, followed by a higher dose to a reduced field that consists of the primary tumor and sites of possible nodal involvement. Intensity-modulated radiotherapy (IMRT) allows for precise delivery of radiotherapy to cancer tissues, reduces toxicity to nearby structures, and is the recommended radiotherapy technique for anal cancer (Rao et al. 2021). The risk of inguinal LN involvement increases with increased tumor size, tumors located below the dentate line, or in patients with N1 disease. It is recommended that inguinal LN be included in the radiotherapy field in most anal cancer patients (Rao et al. 2021). Elective radiation to inguinal lymph nodes and nodes superior to the sacroiliac joint can be omitted in selected patients with early tumors (T1N0) (Ng et al. 2012). The PLATO (PersonaLizing Anal cancer radioTherapy dOse) study is an ongoing non-randomized single protocol umbrella platform trial including ACT3, 4, and 5 trials. The ACT4 trial looks at different radiotherapy doses for early anal cancer (Stage I-IIA) (ISRCTN – ISRCTN88455282: PLATO – Personalising anal cancer radiotherapy dose).

The role of surgery:

- Defunctioning colostomy

A pre-treatment defunctioning colostomy can be required in 10–20% of anal cancer patients to relieve their anorectal pain, fecal incontinence, or both. Patients should be warned that half of these colostomies are not reversed with high rates of fecal incontinence or anal stenosis due to the effect of radiotherapy on the anal sphincter (Glynne-Jones et al. 2014). End colostomy is recommended over loop colostomy as the latter has a higher rate of parastomal hernia. CRT can be started two weeks after the creation of colostomy (Rao et al. 2021).

- Fistulating disease

Perianal fistulas, either malignant or benign, can lead to the development of perianal sepsis during CRT. This can delay treatment and have an unfavorable effect on long-term outcomes. Pre-treatment clinical and radiological assessment of anal cancer should detect the presence of a perianal fistula. In patients with fistulas, a seton should be inserted before stating CRT to reduce the risk of infection. The seton will need to stay in for the duration of treatment, and definitive treatment of the fistula should be delayed until the effect of CRT has subsided (Rao et al. 2021).

- APR as primary treatment

CRT has replaced abdominoperineal resection of the rectum and anal canal (APR) as the primary treatment for most anal cancers. APR might be considered the primary treatment option in some patients. Examples include patients who had previous pelvis radiation, transplant patients on immunosuppressants due to the high risk of interrupted CRT, patients with adenocarcinoma or adenosquamous carcinoma of the anal canal, which are more resistant to radiotherapy, and patients refusing CRT (Rao et al. 2021).

- APR as salvage treatment

After CRT, 5–15% of patients will still have a visible or microscopic disease and need an abdominoperineal resection. Similarly, 10–30% of patients will experience locoregional disease relapse. It is unclear whether residual or recurrent disease carries the worse prognosis, and both groups have a skeptical outcome.

- Local excision for anal margin cancer

Early anal margin cancer (T1N0), representing around 5% of anal cancers, is suitable for local excision. A microscopic >1 mm clear margin is required for "complete excision." This requires a macroscopic resection margin of 0.5–1 cm. Primary closure is associated with an increased risk of wound dehiscence, and plastic surgery reconstruction is usually preferable (Rao et al. 2021). Re-excision of a positive margin is associated with a high recurrence rate and is not recommended.

- Postoperative CRT

Postoperative CRT should be considered through MDT discussion in patients who had local excision of anal canal cancers, patients with a histological margin less than or equal to 1 mm, patients who had a piecemeal excision of anal margin cancers, and patients with high radiological or pathological risks of nodal involvement.

Figures 3 and 4 summarize the recommended algorithm for the management of localized and advanced anal cancer as recommended by the European society of medical oncology (ESMO) (Rao et al. 2021).

Follow-up and Prognosis

- CRT response evaluation

Anal cancer response to CRT is slow, and the optimum interval to evaluate treatment response is 26 weeks based on the data from ACT II trial (James et al. 2013). Complete clinical response is defined as the absence of tumor and/or ulceration on DRE. Examination under general anesthesia might be required in some patients. The assessment also includes clinical evaluation of the inguinal regions and radiological assessment using pelvic MRI and CT scans. While it can be challenging to distinguish treatment-induced edema and fibrosis from persistent disease clinically, tissue biopsies are not routinely recommended 8–12 weeks after CRT. It can be challenging to pathologically determine the treatment-related effects from active disease. The lack of clinical response at three months post CRT does not indicate that salvage surgery is indicated as reassessment at six months, which often reveals a late clinically significant regression (Rao et al. 2021). There is insufficient evidence to recommend routine PET-CT in assessing treatment response (Mahmud et al. 2017).

Persistent or recurrent diseases usually occur within the first 24 months from the completion of CRT. Histological confirmation is required, along with radiological assessment and discussion in specialist MDT. Salvage surgery for residual or recurrent disease will require beyond total mesorectal excision (TME) surgery, and surgical planning should include a thorough radiological assessment of all pelvic compartments. The

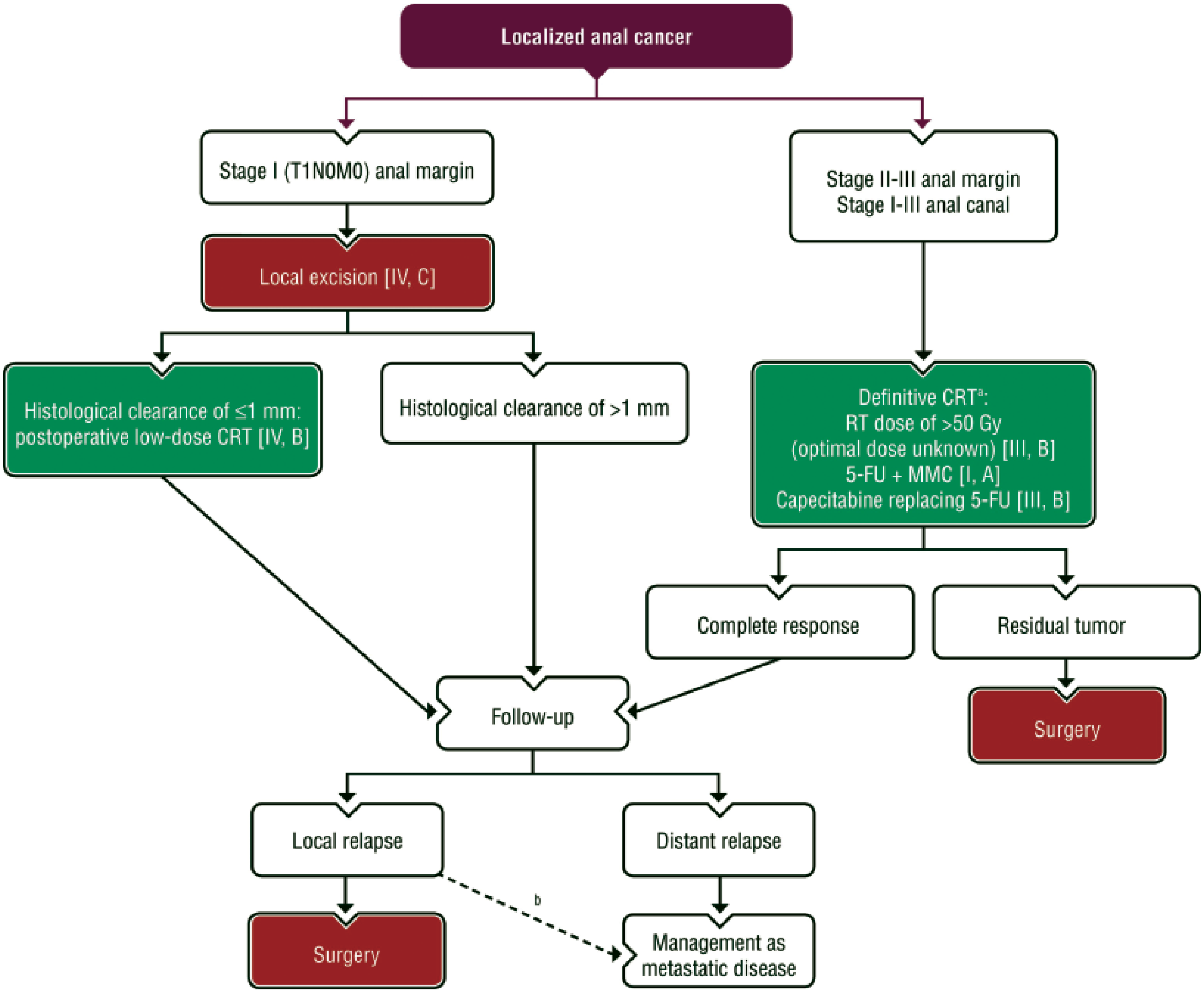
Localized anal cancer
Stage I (T1N0M0) anal margin
Stage II-III anal margin
Stage I-III anal canal
Local excision [IV, C]
Histological clearance of ≤1 mm: postoperative low-dose CRT [IV, B]
Histological clearance of >1 mm
Definitive CRTª:
RT dose of >50 Gy
(optimal dose unknown) [III, B]
5-FU + MMC [I, A]
Capecitabine replacing 5-FU [III, B]
Complete response
Residual tumor
Surgery
Follow-up
Local relapse
Distant relapse
b
Surgery
Management as metastatic disease

Figure 3 Treatment algorithm for localized anal cancer. (Rao et al. 2021/with permission of Elsevier).

Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; M, metastasis; N, node; MMC, mitomycin C; RT, radiotherapy; T, tumor.

(a) Optimum timepoint to assess clinical tumor response after CRT is 26 weeks [II, B].

(b) In cases where surgery cannot be carried out.

mainstay of salvage surgery for tumors involving the anal sphincter complex is APR, and more radical exenterative surgery might be required to achieve an R0 resection. APR for relapsed anal cancer is different from the procedure performed for rectal cancer and plastic perineal reconstruction with musculocutaneous flaps is usually required.

- Advanced/Metastatic disease management

Distant metastatic disease occurs in around 20% of patients. Chemotherapy is commonly a part of treatment because the tumor is typically chemosensitive. Based on the findings from The International Multicentre Study in Advanced Anal Cancer (InterAACT), Carboplatin-paclitaxel is currently recommended as the new standard of care in patients with chemotherapy-naive advanced anal cancer and has replaced the cisplatin – 5FU regimen (Rao et al. 2020).

- Immunotherapy for advanced anal cancer

In addition to HPV viruses' oncogenic abilities, HPV proteins E6 and E7 are known to encourage tumor-infiltrating

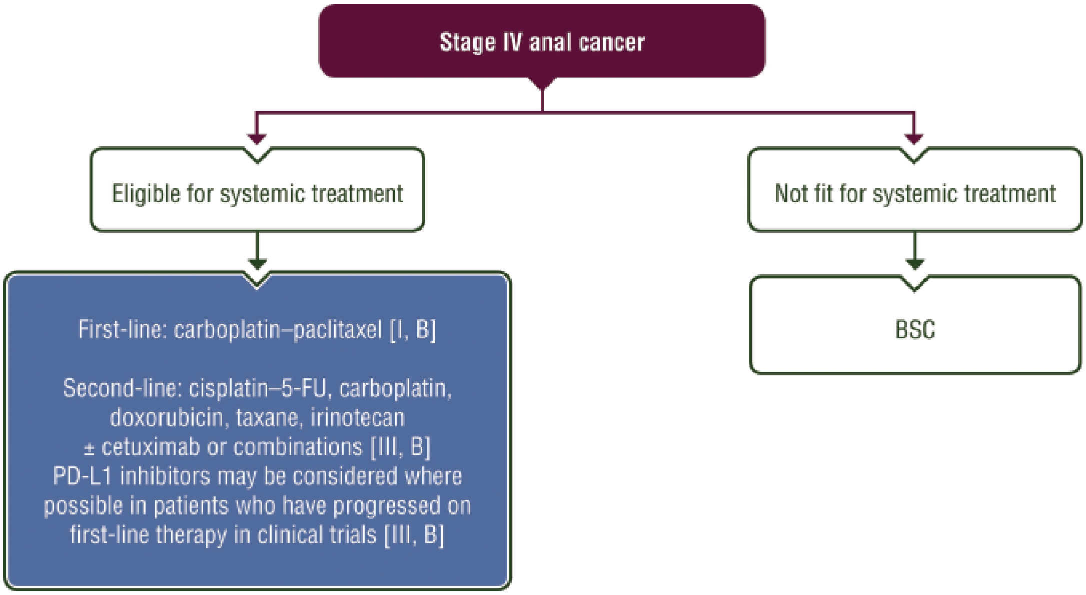
Stage IV anal cancer
Eligible for systemic treatment
Not fit for systemic treatment
First-line: carboplatin–paclitaxel [I, B]
Second-line: cisplatin–5-FU, carboplatin, doxorubicin, taxane, irinotecan ± cetuximab or combinations [III, B]
PD-L1 inhibitors may be considered where possible in patients who have progressed on first-line therapy in clinical trials [III, B]
BSC

Figure 4 Treatment algorithm for advanced anal cancer. (Rao et al. 2021/with permission of Elsevier).

Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
5-FU, 5-fluorouracil; BSC, best supportive care; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

lymphocyte (TILs) recruitment which turns on the immune system's anti-cancer defenses. Given that HPV infection is a known cause of anal cancer, the interest in the role of immunotherapy in advanced anal cancer is growing, especially in patients who progressed while on first-line chemotherapy. The KEYNOTE-028 study reported encouraging results with pembrolizumab, a monoclonal antibody directed against programmed cell death protein 1 (PD-1), in managing a cohort of patients with refractory anal cancer and no other options for standard systemic therapy (Ott et al. 2017). Similar outcomes were reported on the safety and efficacy of nivolumab (Morris et al. 2017). Programmed cell death protein 1 (PD-1)/PD-L1 inhibitor testing and other immunotherapy-based strategies are currently being conducted.

Treatment Complications

As with any chemotherapy regimen, side effects are possible, and a 1–2% mortality risk is present (often from neutropenic sepsis). Up to 30% of individuals who receive radiation therapy or CRT may experience significant late adverse effects such as bleeding, anal necrosis, skin ulceration, stenosis or fibrosis, and diarrhea. Under these circumstances, some individuals might have a colostomy created, either with or without anal resection.

Prognosis

For local control and overall survival in anal cancer, gender, tumor stage, nodal status, and response to chemoradiation are independent prognostic variables (Salmon et al. 1986). Little predictive significance is attached to the histologic subtype. Patients who have malignancies that are well differentiated do better than those who have tumors that are not well differentiated.

Anorectal Malignant Melanoma

Anorectal malignant melanoma is a rare, highly lethal tumor with an incidence of 2.7 per 10 million per year in the United States (Coté and Sobin 2009), and it accounts for 4% of all anal canal tumors (Klas et al. 1999). Delayed diagnosis is common, and almost 60% of patients have distant metastasis on diagnosis (van Schaik et al. 2008) as clinical presentation in the form of perianal itching and bleeding is similar to some common benign proctology conditions such as hemorrhoids. Tumors can look like benign polypoid lesions on endoscopy, especially in the amelanotic melanomas, representing 20–30% of anorectal melanoma.

The pathogenesis of anorectal melanomas is not well established, and there are several theories for the development of melanomas in the gastrointestinal tract, including their development from intestinal Schwann cells and the migration from the neural crest during embryogenesis (Malaguarnera et al. 2018).

The symptoms associated with anorectal melanoma are nonspecific and similar to those related to other more common benign or malignant conditions of the anorectum, like hemorrhoids and rectal cancer. This includes anal pain or discomfort, bleeding, tenesmus, feeling of anal/rectal fullness or mass, change in bowel habits, and even inguinal masses from enlarged LN (Malaguarnera et al. 2018).

Colonoscopy with biopsies followed by histological and immunochemistry assessment is the gold standard diagnostic test for anorectal melanoma. The different forms of melanocytes in anorectal melanomas, including pleomorphic, epithelioid, spindle cells, etc., can resemble other anorectal tumors such as gastrointestinal tumors and sarcomas, indicating the need for immunohistochemical assessment to differentiate between those tumors (Malaguarnera et al. 2018).

The clinical and radiological assessment of anorectal melanomas is similar to the anal squamous cell cancer assessment discussed earlier in this chapter. EUA is helpful for the assessment of tumor site, size, and extent. Radiological tests used for tumor staging include endoanal USS and MRI scans for local staging, while CT scans, MRI liver, and PET/CT are used to detect distal metastasis (Malaguarnera et al. 2018). Anorectal melanoma is staged based on disease spread into stage I (local disease), stage II (spread into regional LN), and stage III (tumors with distant metastasis).

The treatment options for anorectal melanomas include surgical excision, radiotherapy, chemotherapy, immunotherapy, and targeted therapy. While surgery proved to add survival benefit in patients with stage I and Stage II disease, there were no significant survival benefits from surgery in patient with metastatic (stage III) disease (Chen et al. 2016).

Surgical excision in the form of radical abdominoperineal resection (APR) or more conservative wide local excision (WLE), or even endoscopic mucosal resection (EMR), are offered for patients with anorectal melanomas. No clinical trials were performed to compare the outcomes of the radical versus local excision approach. However, recent meta-analyses have shown no survival benefits with more radical excision (APR) than with wide local excision. A less is more approach is recommended to avoid the significant comorbidities associated with APR (Smith et al. 2020; Wanebo et al. 1981). APR is more selectively used now for more local advanced resectable, nonmetastatic tumors not amenable for wide local excision. None of the reported studies compared the quality of life following those two treatment options (Table 4).

Cutaneous melanomas are known to respond well to Immune checkpoint inhibitors such as CTLA-4 (Cytotoxic T-lymphocyte-associated antigen, Ipilimumab) and PD-1 (Programmed-death, Nivolumab, and Pembrolizumab) targeted therapy. However, the evidence of survival benefits in anorectal melanoma still requires more investigation (Adileh et al. 2021).

Patients with anorectal melanomas experience a high rate of disease recurrence with a 5-year disease-free survival of 16–17%, and overall 5-year survival is estimated between 6 and 20% and a median survival of 24 months (Coté and Sobin 2009; van Schaik et al. 2008). Patients with stage I disease (LN negative disease) has significantly better survival (Nusrath et al. 2018). Survival after surgery has not improved over the last three decades (Wanebo et al. 1981). This indicates the need for more studies on other different treatment approaches, such as the potential role of adjuvant targeted therapy and immunotherapy in the management of anorectal melanoma.

Table 4 Overall survival of the surgical treatment (extensive versus local excision) of stage I and II anal melanoma.

Study	No. of patients	Stage	Extensive resection 5 years survival	Local excision 5 years survival	median survival in months
(Jutten et al. 2021)	103	I	13.7%	21.7%	17 / 25 m
		II	8.7%	11.1%	14 / 17 m
(Ford et al. 2018)	570	NS	20.2%	17.3%	
(Nusrath et al. 2018)	20	I	75%	80%	56 m
		II	19%	–	13 m
(Chen et al. 2016)	317	I	18.5%	14.9%	35 / 30 m
		II	14%	22.2%	18 / 23 m
(Wang et al. 2013)	43	NS	27%	0%	28 m
(Zhang et al. 2010)	53	NS	30.7%	16%	25 / 13 m
(Belli et al. 2009)	31	NS	30.7%	22.2%	17 m
(Pessaux et al. 2004)	30	NS	33%	19%	16 m
(Bullard et al. 2003)	15	NS	25%	63.6%	–
(Thibault et al. 1997)	37	NS	23%	36.4%	29 m
(Wanebo et al. 1981)	33	NS	18%	0%	21.5 m
(Pack and Martins 1960)	14	I	11%	100%	–
		II	0%	0%	–

Key Take-Home Management Points

1 Assessment of anal cancer includes careful clinical assessment under GA and obtaining tissue biopsy to be followed by local (MRI) and systemic (CT and PET CT) staging.

2 50% of enlarged inguinal LN patients with anal cancer are reactionary. PET CT or FNA can change the treatment field.

3 Chemoradiotherapy (5-FU + MMC + Radiotherapy) is the current gold standard primary treatment for 80% of patients with anal SCC.

4 The role of surgery in patients with anal cancer includes pre-treatment defunctioning stoma formation, the management of perianal fistulas, APER as primary or salvage treatment, and local excision of small anal margin tumors.

5 The optimal interval to evaluate treatment response following CRT completion is 26 weeks.

6 Persistent or recurrent disease usually occurs in the first 24 months from completion of CRT.

7 Anal melanoma is a rare tumor with a known poor prognosis. The clinical and radiological assessment is similar anal SCC.

8 Staging of anal melanoma, like other melanomas, is based on disease spread into stage I (local disease), stage II (spread into regional LN), and stage III (tumors with distant metastasis).

9 Surgery provides survival benefits to patients with stage I and stage II disease. There is no survival benefit from extensive resection (APR) compared to local excision.

Areas for Further Research

- The role of screening and prevention of anal cancer in high-risk groups.
- Personalized treatment for anal cancer. The role of HPV and immunotherapy.
- The QoL in patients with anal cancer and the impact of different treatment options.

Trusted Websites for Further Reading

- Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up: https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/anal-cancer
- NCCN (National Comprehensive Cancer Network) guidelines on anal cancer: https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
- Surgical treatment of anorectal melanoma: a systematic review and meta-analysis: https://academic.oup.com/bjsopen/article/5/6/zrab107/6446962

References

Adileh, M., Yuval, J.B., Huang, S. et al. (2021). Anorectal Mucosal Melanoma in the era of immune checkpoint inhibition: should we change our surgical management paradigm? *Dis Colon Rectum* 64 (5): 555–562. doi: 10.1097/DCR.0000000000001872.

Ajani, J.A., Winter, K.A., Gunderson, L.L. et al. (2008). Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 299 (16): 1914–1921. doi: 10.1001/jama.299.16.1914.

Bartelink, H., Roelofsen, F., Eschwege, F. et al. (1997). Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 15 (5): 2040–2049. doi: 10.1200/JCO.1997.15.5.2040.

Belli, F., Gallino, G.F., lo Vullo, S. et al. (2009). Melanoma of the anorectal region: the experience of the National Cancer Institute of Milano. *Eur J Surg Oncol* 35 (7): 757–762. doi: 10.1016/j.ejso.2008.05.001.

Brierley, J.D., Gospodarowicz, M.K., and Wittekind, C.. (2017). UICC. TNM classification of malignant tumours, 8th edition due December 2016. *Union for International Cancer Control*. Published online 1–272. https://www.wiley.com/en-gb/TNM+Classification+of+Malignant+Tumours%2C+8th+Edition-p-9781119263579 (accessed 9 March 2022).

Bullard, K.M., Tuttle, T.M., Rothenberger, D.A. et al. (2003). Surgical therapy for anorectal melanoma. *J Am Coll Surg* 196 (2): 206–211. doi: 10.1016/S1072-7515(02)01538-7.

Chen, H., Cai, Y., Liu, Y. et al. (2016). Incidence, surgical treatment, and Prognosis of Anorectal Melanoma from 1973 to 2011: a population-based SEER analysis. *Medicine* 95 (7): e2770. doi: 10.1097/MD.0000000000002770.

Clifford, G.M., Georges, D., Shiels, M.S. et al. (2021). A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. *Int J Cancer* 148 (1): 38–47. doi: 10.1002/IJC.33185.

Coté, T.R. and Sobin, L.H. (2009). Primary melanomas of the esophagus and anorectum: epidemiologic comparison with melanoma of the skin. *Melanoma Res* 19 (1): 58–60. doi: 10.1097/CMR.0b013e32831ef262.

Cummings, B. (1984). Results and toxicity of the treatment of anal canal Carcinoma by radiation therapy or radiation therapy and chemotherapy. *Cancer* 54: 2062–2068. https://doi.org/10.1002/1097-0142(19841115)54:10%3C2062::aid-cncr2820541004%3E3.0.co;2-t (accessed 13 March 2022).

Damin, D.C., Rosito, M.A., and Schwartsmann, G. (2006). Sentinel lymph node in carcinoma of the anal canal: a review. *Eur J Surg Oncol* 32 (3): 247–252. doi: 10.1016/J.EJSO.2005.08.006.

Durot, C., Dohan, A., Boudiaf, M. et al. (2017). Cancer of the anal canal: diagnosis, staging and Follow-Up with MRI. *Korean J Radiol* 18 (6): 946. doi: 10.3348/KJR.2017.18.6.946.

Flam, M., John, M., Pajak, T.F. et al. (2016). Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. 14 (9): 2527–2539. doi:10.1200/JCO.1996.14.9.2527.

Ford, M.M., Kauffmann, R.M., Geiger, T.M. et al. (2018). Resection for anal melanoma: is there an optimal approach? *Surgery* 164 (3): 466–472. doi: 10.1016/J.SURG.2018.05.026.

Gervaz, P., Hirschel, B., and Morel, P. (2006). Molecular biology of squamous cell carcinoma of the anus. *Br J Surg* 93 (5): 531–538. doi: 10.1002/BJS.5376.

GLOBOCAN (2020). https://gco.iarc.fr/today/data/factsheets/cancers/10-Anus-fact-sheet.pdf (accessed 18 February 2022).

Glynne-Jones, R., Kadalayil, L., Meadows, H.M. et al. (2014). Tumour- and treatment-related colostomy rates following mitomycin C or cisplatin chemoradiation with or without maintenance chemotherapy in squamous cell carcinoma of the anus in the ACT II trial. *Ann Oncol* 25 (8): 1616–1622. doi: 10.1093/annonc/mdu188.

Glynne-Jones, R., Meadows, H., Wan, S. et al. (2008). EXTRA–a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. *Int J Radiat Oncol Biol Phys* 72 (1): 119–126. doi:10.1016/J.IJROBP.2007.12.012.

Williams, G.R. and Talbot, I.C. (1994). Anal carcinoma–a histological review. *Histopathology* 25 (6): 507–516. doi: 10.1111/J.1365-2559.1994.TB01370.X.

ISRCTN – ISRCTN88455282: PLATO – Personalising anal cancer radiotherapy dose. https://www.isrctn.com/ISRCTN88455282 (accessed 20 March 2022).

James, R.D., Glynne-Jones, R., Meadows, H.M. et al. (2013). Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial. *Lancet Oncol* 14 (6): 516–524. doi: 10.1016/S1470-2045(13)70086-X (accessed 20 March 2022).

Jutten, E., Kruijff, S., Francken, A.B. et al. (2021). Survival following surgical treatment for anorectal melanoma seems similar for local excision and extensive resection regardless of nodal involvement. *Surg Oncol* 37: 101558. doi: 10.1016/j.suronc.2021.101558.

Klas, J.V., Rothenberger, D.A., Wong, W.D., and Madoff, R.D. (1999). Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 85 (8): 1686–1693. doi: 10.1002/(sici)1097-0142(19990415)85:8<1686::aid-cncr7>3.0.co;2-7.

Maas, M., Tielbeek, J.A.W., and Stoker, J. (2020). Staging of anal cancer: role of MR imaging. *Magn Reson Imaging Clin N Am* 28 (1): 127–140. doi: 10.1016/J.MRIC.2019.09.005.

Mahmud, A., Poon, R., and Jonker, D. (2017). PET imaging in anal canal cancer: a systematic review and meta-analysis. *Br J Radiol* 90 (1080). doi: 10.1259/BJR.20170370.

Malaguarnera, G., Madeddu, R., Catania, V.E. et al. (2018). Anorectal mucosal melanoma. *Oncotarget* 9 (9): 8785–8800. doi: 10.18632/oncotarget.23835.

Morris, V.K., Salem, M.E., Nimeiri, H. et al. (2017). Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *Lancet Oncol* 18 (4): 446–453. doi: 10.1016/S1470-2045(17)30104-3.

Ng, M., Leong, T., Chander, S. et al. (2012). Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. *Int J Radiat Oncol Biol Phys* 83 (5): 1455–1462. doi: 10.1016/J.IJROBP.2011.12.058.

Nigro, N.D., Seydel, H.G., Considine, B. et al. (1983). Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer* 51 (10): 1826–1829. doi: 10.1002/1097-0142(19830515)51:10<1826::AID-CNCR2820511012>3.0.CO;2-L.

Nigro, N.D., Vaitkevicius, V.K., and Considine, B. (1974). Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum* 17 (3): 354–356. doi: 10.1007/BF02586980.

Northover, J.M.A., Arnott, S.J., Cunningham, D. et al. (1996). Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet* 348 (9034): 1049–1054. doi: 10.1016/S0140-6736(96)03409-5.

Nusrath, S., Thammineedi, S.R., Patnaik, S.C. et al. (2018). Anorectal malignant melanoma-defining the optimal surgical treatment and prognostic factors. *Indian J Surg Oncol* 9 (4): 519–523. doi: 10.1007/S13193-018-0791-1.

Ott, P.A., Elez, E., Hiret, S. et al. (2017). Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol* 35 (34): 3823–3829. doi: 10.1200/JCO.2017.72.5069.

Pack, G.T. and Martins, F.G. (1960). Treatment of anorectal malignant melanoma. *Dis Colon Rectum* 3 (1): 15–24. doi: 10.1007/BF02616493.

Papillon, J. and Montbarbon, J.F. (1987). Epidermoid carcinoma of the anal canal. A series of 276 cases. *Dis Colon Rectum* 30 (5): 324–333. doi: 10.1007/BF02555448.

Peiffert, D., Tournier-Rangeard, L., Gérard, J.P. et al. (2012). Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. *J Clin Oncol* 30 (16): 1941–1948. doi: 10.1200/JCO.2011.35.4837.

Pessaux, P., Pocard, M., Elias, D. et al. (2004). Surgical management of primary anorectal melanoma. *Br J Surg* 91 (9): 1183–1187. doi: 10.1002/bjs.4592.

Rao, S., Guren, M.G., Khan, K. et al. (2021). Anal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up☆. *Ann Oncol* 32 (9): 1087–1100. doi: 10.1016/J.ANNONC.2021.06.015.

Rao, S., Sclafani, F., Eng, C. et al. (2020). International rare cancers initiative multicenter randomized phase II trial of cisplatin and fluorouracil versus carboplatin and paclitaxel in advanced anal cancer: interAAct. *J Clin Oncol* 38 (22): 2510–2518. doi: 10.1200/JCO.19.03266.

Salmon, R.J., Zafrani, B., Labib, A. et al. (1986). Prognosis of cloacogenic and squamous cancers of the anal canal. *Dis Colon Rectum* 29 (5): 336–340. doi: 10.1007/BF02554126.

Sauter, M., Keilholz, G., Kranzbühler, H. et al. (2016). Presenting symptoms predict local staging of anal cancer: a retrospective analysis of 86 patients. *BMC Gastroenterol* 16: 1. doi: 10.1186/S12876-016-0461-0.

Smith, H.G., Glen, J., Turnbull, N. et al. (2020). Less is more: a systematic review and meta-analysis of the outcomes of radical versus conservative primary resection in anorectal melanoma. *Eur J Cancer* 135: 113–120. doi: 10.1016/j.ejca.2020.04.041.

Thibault, C., Sagar, P., Nivatvongs, S. et al. (1997). Anorectal melanoma–an incurable disease? *Dis Colon Rectum* 40 (6): 661–668. doi: 10.1007/BF02140894.

van Schaik, P.M., Ernst, M.F., Meijer, H.A., and Bosscha, K. (2008). Melanoma of the rectum: a rare entity. *World J Gastroenterol: WJG* 14 (10): 1633. doi: 10.3748/WJG.14.1633.

Wanebo, H.J., Woodruff, J.M., Farr, G.H., and Quan, S.H. (1981). Anorectal melanoma. *Cancer* 47 (7): 1891–1900. doi: 10.1002/1097-0142(19810401)47:7<1891::aid-cncr2820470730>3.0.co;2-k.

Wang, M., Zhang, Z., Zhu, J. et al. (2013). Tumour diameter is a predictor of mesorectal and mesenteric lymph node metastases in anorectal melanoma. *Colorectal Dis* 15 (9): n/a–n/a. doi: 10.1111/codi.12250.

Wieland, U. and Kreuter, A. (2019). Anal cancer risk: HPV-based cervical screening programmes. *Lancet Infect Dis* 19 (8): 799–800. doi: 10.1016/S1473-3099(19)30296-8.

Zhang, S., Gao, F., and Wan, D. (2010). Abdominoperineal resection or local excision? a survival analysis of anorectal malignant melanoma with surgical management. *Melanoma Res* 20 (4): 338–341. doi: 10.1097/CMR.0b013e328339b159.

Section III Hepatobiliary and Pancreas Cancer

14 Epidemiology and Risk Factors of Hepatocellular Carcinoma

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Global Incidence of Hepatocellular Carcinoma

Overview

Worldwide, primary liver cancer is the seventh most common cancer and the fourth most common cause of cancer mortality (Freddie Bray et al. 2018). Globally, over 840,000 people develop liver cancer each year, and 780,000 die of it. More than 70% of deaths occur in men. (Mohammadian et al. 2020). However, liver cancer burden is not evenly distributed throughout the world (Figure 1). Most cases of hepatocellular carcinoma (HCC) occur in either Africa or Asia. Mongolia has the single highest incidence rate, with an age-standardized rate of 94.7/100,000 person-years (Petrick and McGlynn 2019).

North and South America, Northern Europe, and Oceania are low-rate areas for liver cancer (5.1–6.9/100,000) among most populations. The rates in Latin America and the Caribbean are nearly double (11.4/100,000). However, incidence rates are increasing in areas previously thought to have low rates. Liver cancer incidence rates are more than two-fold higher in males than females in most regions of the world [US (male: 8/100,000, female: 2.7/100,000), Europe (male: 10.1/100,000, female: 3.7 /100,000), Oceania (male: 17.1/100,000, female 5.9/100,000), Africa (male: 12/100,000, female: 5.3/100,000), Latin America and the Caribbean (male: 12/100,000, female: 5.3/100,000)]. In Asia, the difference is attenuated (male: 6.1/100,000; female: 4.1/100,000) (Mohammadian et al. 2020).

HCC accounts for more than 75% of primary liver cancer (Petrick et al. 2020). One noteworthy exception is the Khon Kaen region of Thailand, which has one of the world's highest rates of liver cancer (age-standardized rate from 1993–1997 male: 88.0/100,000; female: 35.4/100,000). This disease burden is due to endemic infestation with liver flukes, so the major type of liver cancer in this region is intrahepatic cholangiocarcinoma (Okuda et al. 2002).

Encouraging trends in liver cancer incidence have been seen in some high-rate areas (Valery et al. 2018). Between 1978 and 2012, incidence decreased in multiple Asian countries and southern Europe like Spain and Italy. The rates may have plateaued in the US but have increased in countries with historically low rates, including Oceania (Figure 2) (McGlynn et al. 2021) (Valery et al. 2018).

Decreasing rates in Asia are likely due to hepatitis B virus (HBV) vaccination programs. In Taiwan, a national newborn vaccination began in 1984. HCC incidence declined 80% and mortality declined 92% in children born after the vaccination program began (C.-L. Lin and Kao 2020). China, Singapore, and Spain implemented similar programs, resulting in decreased incidence of HCC among children. (McGlynn et al. 2015). It is too early to expect an impact on HCC incidence on adults, therefore the impact on HCC incidence among people less than 18 are reported. Other public health measures could have contributed to declines in HCC incidence in high-risk areas of China. A Chinese government program started in the late 1980s to shift the staple diet of the Jiangsu Province from corn to rice has limited hepatocarcinogen aflatoxin B_1 (AFB_1) exposure in this area (Chen et al. 2013; Sun et al. 2013). Similarly, another Chinese public health campaign initiated in the early 1970s to encourage drinking of well water rather than pond or ditch water could have decreased consumption of microcystins, cyanobacteria-produced compounds shown to be hepatocarcinogenic in experimental animals (Yu n.d.).

In contrast, registries in several low-rate areas reported increases in HCC incidence between 1978–1982 and 1993–1997. These registries include the US, UK, and Australia. The increased incidence in low-rate areas may be related to an increased prevalence of hepatitis C virus (HCV) infection in these areas. However, reasons for the decreased incidence in high-rate areas and the increased incidence in low-rate areas are not yet clear, emphasizing the important of conducting case studies in these areas.

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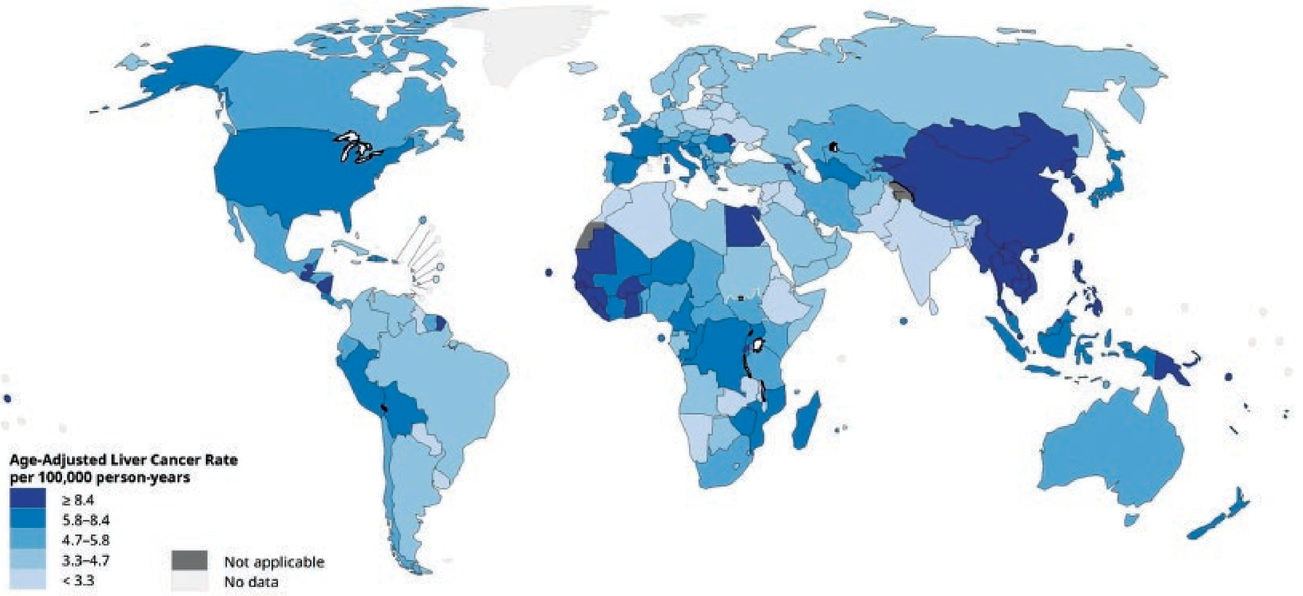


Figure 1 Regional variations in incidence rates of HCC categorized by age-adjusted incidence rates for 2018. Data source: GLOBOCAN 2018. Graph production: IARC (http://gco.iarc.fr/today), World Health Organization.

Race/Ethnicity

HCC incidence rates vary widely among different populations living in the same region. For example, ethnic Indian, Chinese, and Malay populations in Singapore had age-adjusted rates ranging from 21.21/100,000 among Chinese males to 7.86/100,000 among Indian males between 1993 and 1997. Conversely, rates within an ethnic group can vary by geographic location. Populations of ethnic Chinese patients in China have higher incidence than those outside China (McGlynn et al. 2015). Evaluation of the California Cancer Registry showed foreign-born Chinese, Korean, and Vietnamese patients had higher incidence of HCC than US-born patients of the same ethnic groups. In the US between 2006 and 2010, Asian and Pacific Islanders had an incidence rate of 9.8–11.7/100,000 (McGlynn et al. 2021; Sangaramoorthy et al. 2020). The reasons for this interethnic variability likely include differences in the prevalence and acquisition time of major risk factors for liver disease and HCC. In the US, Hispanic and Black patients have almost two-fold higher HCC incidence versus white patients (9.8/100,000 and 8.1/100,000 vs 4.6/100,000, respectively). Despite some differences related to genetic risk factors, these differences are more likely to be driven by socioeconomic determinants than biologic, including genetics, processes (McGlynn et al. 2021).

Gender

In almost all populations, males have higher liver cancer rates than females, with male:female ratios averaging between 2:1 and 4:1. The highest ratios are seen in Europe [France (male:female ratio = 5:0), Malta (male:female ratio = 4:8)] (Petrick and McGlynn 2019). However, several countries in Africa and central and South America have a nearly equal male:female ratio [Uganda (male:female ratio = 1.1), Costa Rica (male:female ratio = 1.6), and Ecuador (male:female ratio = 1.0)]. In addition, rates of HCC in men in the US younger than 50 have declined (X. Zhang et al. 2020). While estrogen could have a protective effect for HCC, men over 70 years have a three-fold higher rate of HCC compared with post-menopausal women (X. Zhang et al. 2020).

The reasons for higher rates of liver cancer in males could relate to gender-specific differences in exposure to risk factors. Men are more likely to be infected with HBV and HCV and tend to consume more alcohol and smoke cigarettes than women. The declining rates of HCC in men parallel declining rates of HCV. Higher androgenic hormone levels and increased body mass index (BMI) could also adversely affect male risk.

Age

Many factors contribute to variations in global age distribution of patients with HCC, including gender, region, and etiology of liver disease (El-Serag and Rudolph 2007). For developed countries considered low risk, the highest rates of HCC were in men between 75–80 years of age and in women 80–85 years of age. In high-risk regions, HCC cases were highest in those 50–59 years old (Sharma 2020). In some high-risk regions, such as Haimen, China, rates among men are bimodal, with peaks at ages 50 and 80 years (F. Bray et al. 2017). These variable age-specific patterns are likely related to differences in the dominant hepatitis virus in the population, the age at viral infection,

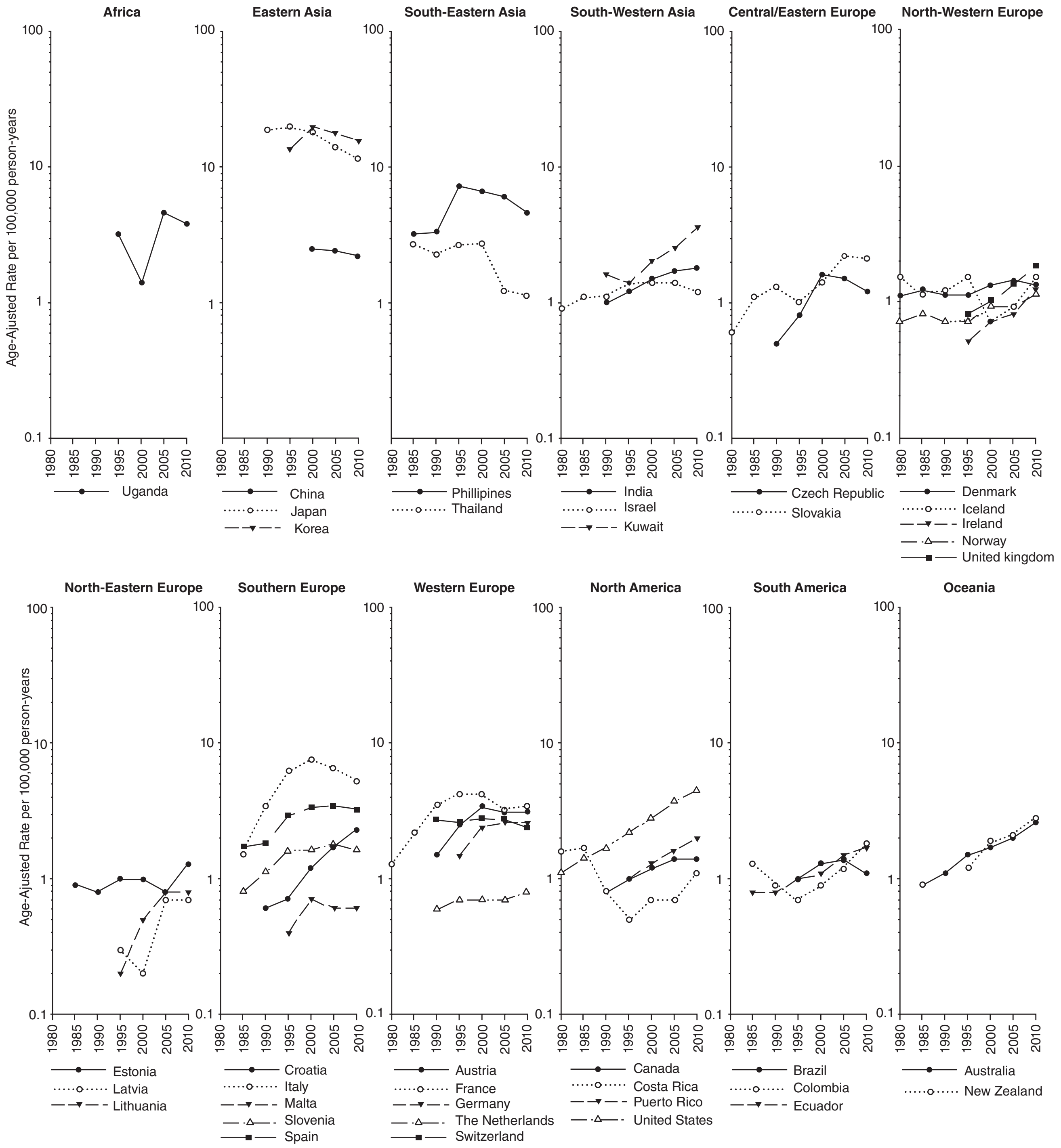


Figure 2 Trends in hepatocellular carcinoma incidence rates by country, 1978–1982 through 2008–2012. Rates are per 100,000 person-years and age-adjusted to the world standard population. Adapted from McGlynn et al. (2021).

and other risk factors. Notably, while most HCV carriers become infected as adults, most HBV carriers are infected at a very young age.

Distribution of HCC Risk Factors

Major risk factors for HCC vary by region. In most high-risk areas, the dominant risk factor is chronic HBV infection. In Asia, HBV is largely acquired by maternal transmission, whereas sibling-to-sibling transmission at young ages is more common in Africa. Consumption of AFB_1-contaminated foods is another major HCC risk factor in most high-rate areas. Unlike most of Asia, the dominant hepatitis virus in Japan is HCV, which began to circulate shortly after World War II (Yoshizawa 2002). Consequently, HCC rates increased sharply in the mid-1970s peaked around 2010 and started declining after that.

In low-rate HCC areas, the dominant risk factors for HCC include cirrhosis due to HCV and, to a lesser extent alcoholic and non-alcoholic fatty liver disease, as well as a general improvement in survival among cirrhosis patients. HCV began to infect large numbers of young adults in North America and South and Central Europe in the 1960s and 1970s due to injection drug use (Armstrong et al. 2000). The virus then moved into national blood supplies and circulated until a screening test was developed in 1990, after which rates of new infection dropped dramatically. Currently, it has been estimated that HCV-related HCC in low-rate countries peaked around 2020 (El-Serag and Kanwal 2014; Petrick et al. 2016).

HCC in the United States

Age-adjusted HCC incidence rates increased more than two-fold between 1985 and 2002 (El-Serag et al. 2004). However, the rate of increase slowed between 2009–2013 (Kim and El-Serag 2019). Recent changes in management of risk factors, including novel agents for treating and managing HBV and HCV infection have contributed to this reduced rate increase. However, regions in the US, such as Texas, have rising incidence (9.7/100000) that primarily affects the Hispanic population (Kim and El-Serag 2019). In recent years as incidence rates increased, the age distribution of HCC patients has skewed relatively younger, with the greatest proportional increases between the ages of 45 and 60. Between 1999 and 2016, HCC-related deaths increased from 5,112 to 11,073 (Kim and El-Serag 2019).

Risk Factors of Hepatocellular Carcinoma

HCC largely occurs within an established background of chronic liver disease and cirrhosis (approximately 70–90% of all detected HCC cases). Major causes of cirrhosis in patients with HCC include HBV, HCV, alcoholic liver disease, and non-alcoholic steatohepatitis.

Hepatitis B Virus

Globally, HBV is the most frequent underlying cause of HCC with an estimated 240–350 million persons with chronic infection worldwide (McGlynn et al. 2015). HBV DNA is found in the host genome of infected and malignant hepatic cells. Thus, HBV could initiate malignant transformation through a direct carcinogenic mechanism by increasing the likelihood of viral DNA insertion in or near proto-oncogenes or tumor suppressor genes. Chronic HBV carriers have a 10–25% lifetime risk of HCC. Between 70% and 90%, of HBV-related HCC develops in a background of cirrhosis (Kulik and El-Serag 2019). The annual HCC incidence is 0.42% in chronic HBV carriers in the US and 0.6% and 3.7% in HBV carriers without and with cirrhosis in east Asia, respectively (El-Serag 2012; McGlynn et al. 2021).

The increased HCC risk associated with HBV infection particularly applies to areas where HBV is endemic. In these areas, HBV is usually transmitted from mother to newborn (vertical transmission) with up to 90% of infected persons experiencing chronic infection (El-Serag 2012). This pattern is different in areas with low HCC incidence rates where HBV is acquired in adulthood through sexual and parenteral routes (horizontal transmission) with >90% of acute infections resolving spontaneously.

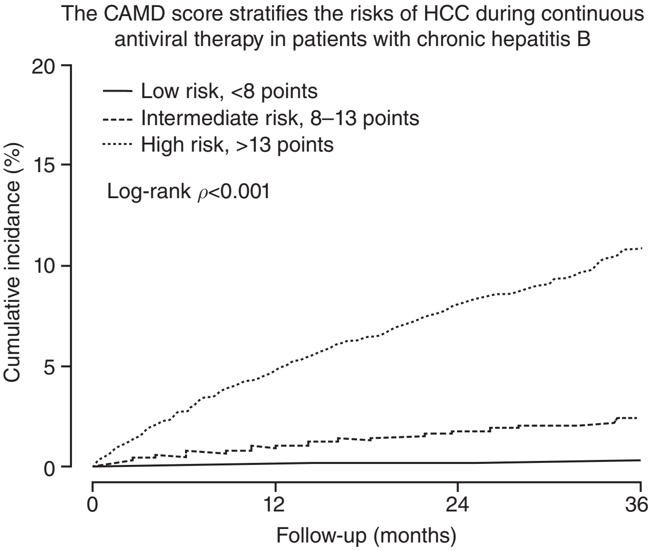
Several other factors have been reported to increase HCC risk among HBV carriers. These include male gender, older age, longer duration of infection, Asian or African race, cirrhosis, family history of HCC, exposure to AFB_1, alcohol or tobacco use, or coinfection with HCV, HIV or hepatitis delta virus. HCC risk is also increased in patients with higher levels of HBV replication, as indicated by presence of hepatitis B e antigen and high HBV DNA levels. It has been suggested in Asian studies that genotype C is associated with more severe liver disease than genotype B (McGlynn et al. 2015). Some risk factors have been incorporated into scoring systems or surveillance recommendations, such as CAMD score (Figure 3), and the one devised by the American Association for the Study of Liver Diseases based on cirrhosis, family history of HCC, age, and Asian or African American race/ethnicity.

HBV vaccination programs are the key HCC prevention strategy. In Taiwan, HCC incidence declined 80% and mortality declined 92% in cohorts born after the vaccination program began (El-Serag and Kanwal 2014). Many other countries that implemented programs in the 1980s, such as China, Singapore, and Spain are seeing reductions similar to those of Taiwan in the prevalence of HBV in vaccinated cohorts (Gordon et al. 2014).

In the natural history of chronic HBV infection, spontaneous or treatment-induced development of antibodies against

The simple formula of the CAMD score

Variable	Risk score
Cirrhosis	
No cirrhosis	0
Cirrhosis with age <40 yr	10
Cirrhosis with age ≥40 yr	6
Age	
Age <40 yr	0
Age 40–49 yr	5
Age 50–59 yr	8
Age 60 yr or older	10
Gender	
Female sex	0
Male sex	2
Diabetes mellitus	
Not diabetic	0
Diabetic	1



The CAMD score stratifies the risks of HCC during continuous antiviral therapy in patients with chronic hepatitis B

Figure 3 Cirrhosis, Age, Male, Diabetes (CAMD) model for predicting the risk of developing future hepatocellular carcinoma among patients with chronic HBV who are receiving oral antiviral treatment.

hepatitis B surface antigen and hepatitis B e antigen or consistently lower level of viral load measured by HBV DNA leads to improved clinical outcomes. Randomized controlled trials have shown that antiviral treatment of HBV infection can achieve sustained reductions in HBV-DNA levels and improve liver function and histology (World Health Organization 2015). A meta-analysis found that HBV treatment with the nucleoside analogs, significantly lowers HCC incidence by 3.6% (6.4%vs 2.8%) (Papatheodoridis et al. 2010). Entecavir or tenofovir, both nucleoside reverse transcriptase inhibitors, are the current first line treatments are also associated a significant reduction in HCC risk. The 5-year cumulative incidence of HCC in enectavir or tenfovir was 0.5–6.9% in patients without cirrhosis, 4.5–21.6% in compensated cirrhosis, and 36.3–46.5% in decompensated cirrhosis (Tseng et al. 2020).

Using sensitive amplification assays, many studies have demonstrated that HBV DNA persists as an “occult HBV infection” for decades among persons with serological recovery from acute infection (i.e., hepatitis B surface antigen negative). Occult HBV is associated with antibodies to hepatitis B core and/or surface proteins (El-Serag 2012). However, in a significant proportion of individuals, neither antibody can be detected. A systematic review of 16 studies found a small association with HCC in four longitudinal studies but this was overestimated due to an erratum in one of the included studies. The remaining studies found no association; however, they were limited by small numbers of cases. Currently, there is no conclusive evidence that occult HBV infection increases HCC risk (El-Serag 2012; X. Huang and Hollinger 2014).

Hepatitis C Virus

Chronic HCV infection is a major risk factor for HCC development. HCV is an RNA virus that does not integrate into the host’s genome and is, thus, unlikely to be the primary initiator of tumorigenesis. Rather, as approximately 90% of HCV associated HCC cases are preceded by cirrhosis, HCV likely promotes tumorigenesis through repetitive damage, regeneration, and fibrosis (Davis et al. 2010). Chronic HCV is associated with a 15–20-fold increase in HCC (Donato et al. 2002). Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1–4%. The proportion of HCV infection markers in HCC cases are found in 44–66% of HCC cases in Italy (Fasani et al. 1999; Stroffolini et al. 1999), 27–58% of cases in France, 60–75% of cases in Spain, and 80–90% of cases in Japan (Yoshizawa 2002).

Factors that increase the risk of HCC include male sex, older age, Hispanic ethnicity, heavy alcohol intake, tobacco smoking, diabetes, obesity, and coinfection with HIV or HBV. Viral factors such as HCV genotype 3, duration of infection, and presence of viremia are also associated with increased risk (McGlynn et al. 2021; Morgan et al. 2013; Petrick et al. 2016).

The advent of direct acting antiviral agents has led to widespread treatment of HCV infection. Sustained virologic response (SVR) has been shown to decrease the risk of HCC by 50–80% (Ioannou et al. 2017) but not to baseline especially in patients with advanced fibrosis or cirrhosis. Patients with SVR have an HCC incidence of 0.24 per 100 person years in patients without cirrhosis and 1.97 per 100 person years in patients with cirrhosis. These incidence rates are at, or below, the threshold for cost-effective HCC surveillance (Figure 4) (Ioannou et al. 2017; Kanwal et al. 2018).

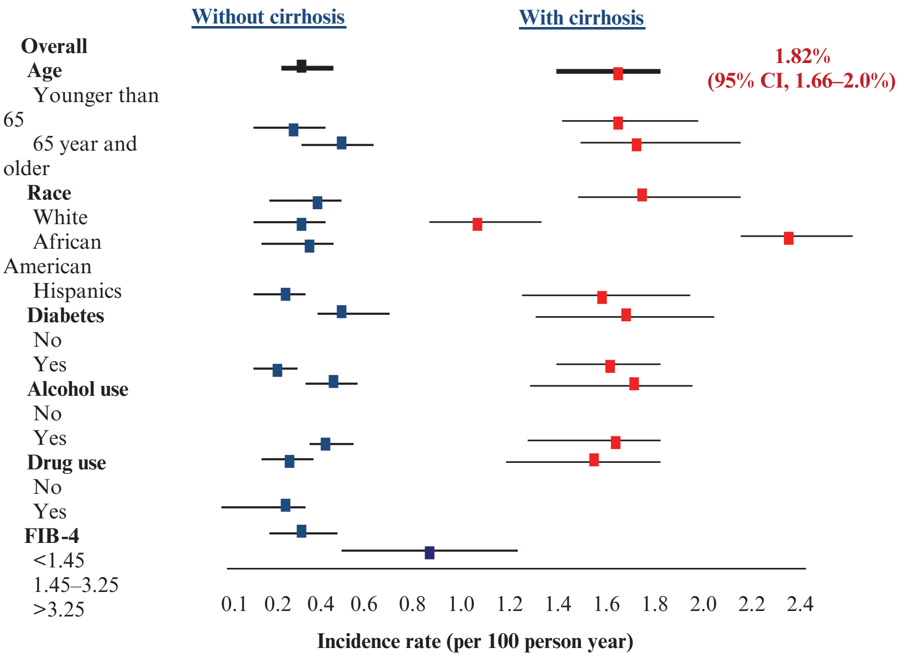


Figure 4 Annual incidence of HCC after DAA-related SVR Stratified by cirrhosis. Adapted from Kanwal F, Gastroenterology 2018.

Alcohol

Heavy alcohol intake, defined as ingestion of >50–70 g/day for prolonged periods, is a well-established HCC risk factor. It is unclear if risk of HCC is significantly altered in those with low or moderate alcohol intake (Park et al. 2020). A meta-analysis of prospective studies found there was no association between HCC and lower levels of alcohol consumption (<3 drinks/day) (Turati et al. 2014); however, a pooled analysis of prospective studies showed this same level was associated with a significantly decreased risk of HCC even after excluding non-drinkers. The latter study found no association between risk and lower-level consumption among persons with diabetes but found 35% decreased risk among persons without diabetes (Petrick et al. 2018). Alcohol use could have a stronger association with HCC risk among women than men. In a meta-analysis examining heavy drinking (>4 drinks/day), alcohol was associated with a 1.6-fold increased risk of HCC among men but an almost 4-fold increase in risk among women. This could be due to differences in alcohol dehydrogenase activity or a stronger association between alcohol and cirrhosis among women (Frezza et al. 1990, 1992).

There is also evidence for a synergistic effect of heavy alcohol ingestion with HCV or HBV. These factors presumably increase HCC risk by collectively promoting cirrhosis. For example, Donato et al. (2002) reported that among alcohol drinkers, HCC risk increased linearly with a daily intake >60 g. However, the concomitant presence of HCV infection led to an additional two-fold increase in HCC risk over that observed with alcohol usage alone (i.e., a positive synergistic effect).

Aflatoxin

Aflatoxins are mycotoxin produced by the *Aspergillus* fungus. This fungus grows on foodstuffs like corn, maize, and peanuts stored in warm, damp conditions. AFB1 occurs in many locations around the world, especially in countries with warm, humid environments. Of the four principal aflatoxins, B1, B2, G1, and G2, the most potent is aflatoxin B1 (AFB1) (Alberg et al. 2014). Animal experiments showed that AFB_1 is a powerful hepatocarcinogen, leading the International Agency for Research on Cancer (IARC) to classify it as carcinogenic ("Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42" 1987).

Once ingested, AFB_1 is metabolized to an active intermediate, AFB_1-*exo*-8,9-epoxide, that binds DNA and causes damage, such as producing the characteristic serine 249 mutation in the p53 tumor suppressor gene (Garner et al. 1972). This mutation has been observed in 30–60% of HCC tumors in AFB_1-endemic areas(Bressac et al. 1991; Turner et al. 2002).

Strong evidence that AFB_1 is an HCC risk factor. These studies were possible due to the development of assays for AFB_1 metabolites in urine and AFB_1-albumin adducts in serum as well as detection of the signature AFB_1 DNA mutation in tissues.

AFB1 is particularly carcinogenic when it co-occurs with chronic HBV infection A meta-analysis estimated that AFB1 alone increased HCC risk by 6-fold, HBV alone by 11-fold, and the two factors together by 54-fold (Liu et al. 2012). In most areas where AFB_1 exposure is a problem, chronic HBV infection is highly prevalent. HBV vaccination in these areas should be the primary preventive tactic; however, chronically infected persons will not benefit from vaccination. These individuals could benefit from eliminating AFB_1 exposure. AFB1 contamination of crops is difficult to combat because contamination can occur both pre- and post-harvest (Udomkun et al. 2017). A successful effort was the replacement of maize with rice as the dietary staple in parts of China; these efforts are credited at least partly for recent declines in liver cancer incidence and mortality (Chen et al. 2013; Sun et al. 2013).

Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD has become one of the most common causes of liver disease globally (Cheemerla and Balakrishnan 2021). NAFLD is the hepatic manifestation of metabolic syndrome, often co-existing with diabetes, hypertension, and obesity. Its prevalence has doubled in the US to 30% of the population in the last 20 years, paralleling the obesity epidemic, NAFLD is now a leading cause of cirrhosis and NASH is the second-leading cause of liver transplantation related to HCC in the US (Liu et al. 2012).

NAFLD represents a broad spectrum of histologic severity; so HCC incidence should be considered in the context of distinct histologic stages. Most NAFLD is of the nonalcoholic fatty liver subtype (NAFL, simple steatosis), which is characterized by hepatocyte fat accumulation without necroinflammation and low risk of fibrosis progression. Up to 30% of NAFLD cases are of the non-alcoholic steatohepatitis (NASH) category, which is characterized by necroinflammation and is associated with fibrosis progression.

The risk of HCC in NAFLD background ranges from 0 to 38% over a follow-up of 5–10 years. A large US Veterans Affairs NAFLD cohort study reported an HCC incidence of 0.21 per 1000 person-years among patients with NAFLD, which was significantly higher than controls without NAFLD (Kanwal et al. 2018). The incidence of HCC is highest among people with NAFLD-related cirrhosis, ranging from 2.4 to 12.8%(D. Q. Huang et al. 2021) (instead you could say 10–15 per 1000 person-years). However, this risk is substantially different depending on NAFLD subtype. A recent meta-analysis of 16 studies reported an incidence rate of 0.03 per 1000 person-years in non-cirrhotic patients and 3.78 per 100 person-years in patients with NASH cirrhosis (Orci et al. 2021). Individual studies have reported an HCC incidence ranging from 0.08 to 0.62 per 1000 patient years among NAFLD populations excluding cirrhosis (Adams et al. 2005; Kawamura et al. 2012; Mittal et al. 2016; Sorensen et al. 1998; White et al. 2012). It should be noted that while 20–30% of NAFLD-related HCCs develop in the absence of cirrhosis, this still represents a rare event (Udomkun et al. 2017).

Factors related to HCC risk associated with NAFLD include clinical factors (cirrhosis, diabetes, obesity, hypertension), demographic characteristics (age, race/ethnicity) (Figure 5), and genetic susceptibility (e.g., genetic variability in PNPLA3). In addition, diabetes or insulin resistance, obesity, older age, and male gender conferred an increased risk (Younossi and Henry 2021). It is unclear whether HCC risk in NAFLD is mediated by the presence of metabolic traits, such as diabetes and hypertension, or through the direct necroinflammatory effects confers an increased risk compared with patients

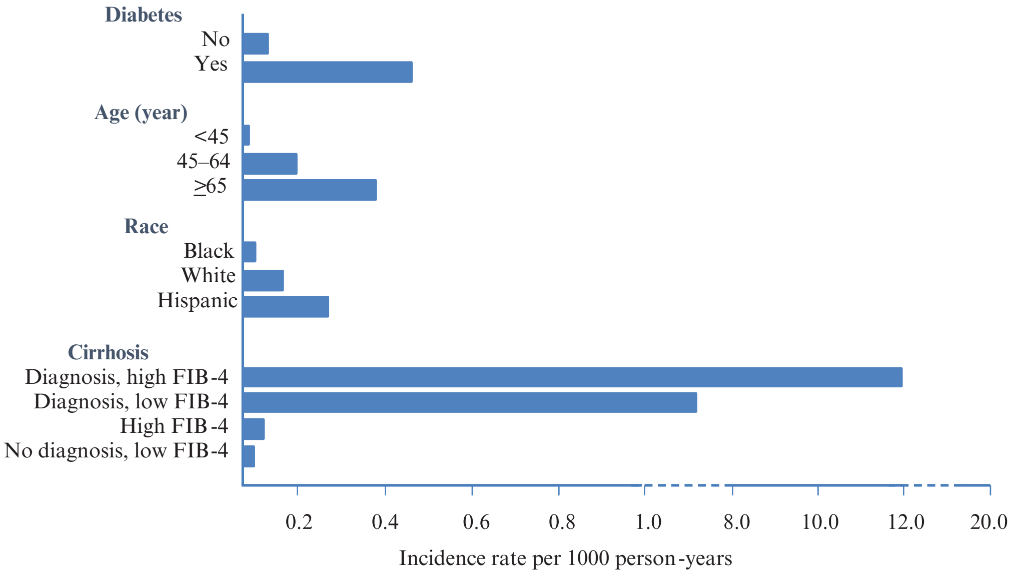


Figure 5 HCC Incidence in Subgroups of Patients with NAFLD. (Source Kanwal et al. Gastroenterology 2018).

without these comorbidities. While weight loss can reduce NAFLD severity, no studies have demonstrated that weight loss is associated with a reduction in HCC risk.

HCC screening is recommended among patients with NAFLD cirrhosis (Figure 6). This recommendation is based on cost-effectiveness modeling that concluded a benefit based on an annual HCC incidence in NAFLD cirrhosis ≥1.5% (Marrero et al. 2018). There is no high-level evidence to support or refute the value, method, or frequency of HCC surveillance among the NAFLD population.

Obesity

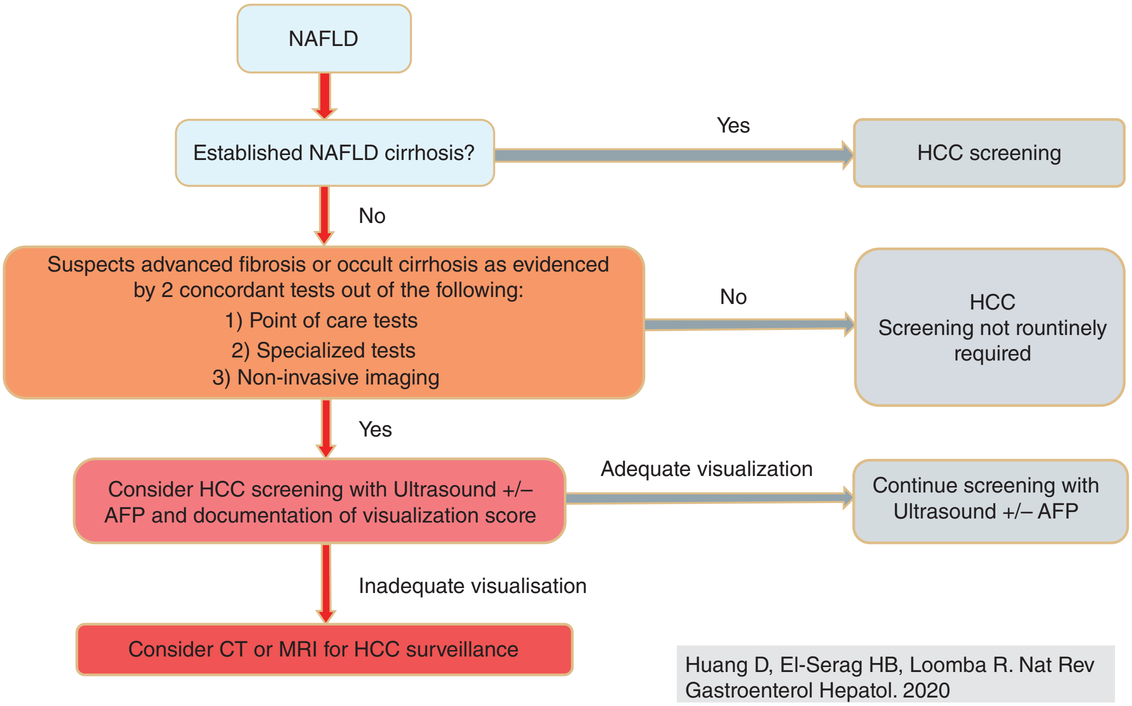
In adults, greater adiposity has been shown to slightly increases risk of liver cancer (Lauby-Secretan et al. 2016). BMI may not accurately capture important elements of obesity, thus studies have examined waist and hip circumference as measures of excess abdominal and gluteofemoral adiposity, respectively. US and European cohort studies found a two-fold increase in HCC risk among those with high waist circumference, and this difference remained when accounting for BMI and hip circumference (Campbell et al. 2016; Florio et al. 2020; Schlesinger et al. 2013). One study indicated that among people with normal or low weight, abdominal size but not gluteofemoral size was associated with increased HCC risk (Florio et al. 2020).

There may be a stronger effect of adiposity that develops at earlier ages. A study out of Denmark found a one-unit increase in BMI z-score at 7 or 13 years of age was associated with a 20–30% increased risk of liver cancer (Berentzen et al. 2014). US and Swedish studies found that obesity in late adolescence and early adulthood was associated with two- to three-fold increase in HCC risk compared to BMI 18–25 (Hagström et al. 2018; B. Yang et al. 2017).

Diabetes Mellitus

Increasing evidence suggests that metabolic syndrome, a collection of conditions including insulin resistance, abdominal obesity, atherogenic dyslipidemia, and hypertension, increases risk of HCC. A 2014 meta-analysis estimated that metabolic syndrome was associated with an 81% increased risk (Ohkuma et al. 2018). Treating one of the metabolic syndrome conditions, dyslipidemia, with statins, however, may ameliorate risk by 37–42% (Franciosi et al. 2013; Singh et al. 2013).

Type 2 diabetes may confer HCC risk via development of NASH/cirrhosis or indirectly via increased levels of insulin and insulin-like growth factors, which are potentially cancer-promoting factors. Case-control studies from the US, Greece, Italy, Taiwan, and Japan have reported mixed findings regarding the association between diabetes, primarily type 2, and HCC (Davila 2005; La Vecchia et al. 1997). However, it is important to remember that cross-sectional and case-control studies are limited by potential reverse causation: approximately 10–20%


NAFLD
Established NAFLD cirrhosis?
Yes
HCC screening
No
Suspects advanced fibrosis or occult cirrhosis as evidenced by 2 concordant tests out of the following:
1) Point of care tests
2) Specialized tests
3) Non-invasive imaging
No
HCC Screening not rountinely required
Yes
Consider HCC screening with Ultrasound +/– AFP and documentation of visualization score
Adequate visualization
Continue screening with Ultrasound +/– AFP
Inadequate visualisation
Consider CT or MRI for HCC surveillance

Huang D, El-Serag HB, Loomba R. Nat Rev Gastroenterol Hepatol. 2020

Figure 6 Screening for HCC in NAFLD. Huang, D et al. 2021 / Springer Nature.

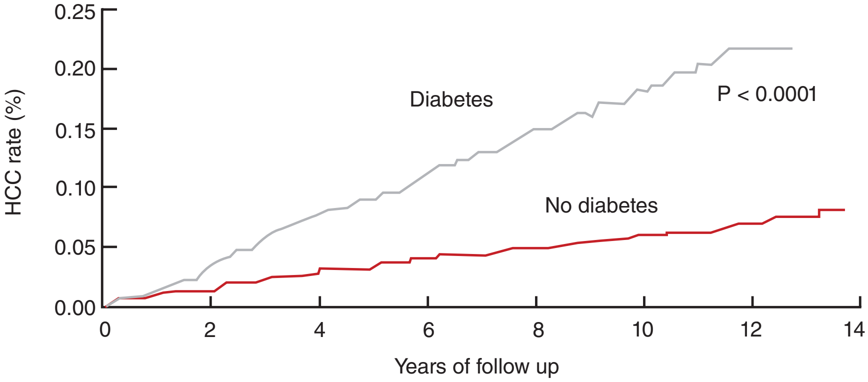


Figure 7 The cumulative incidence of HCC among US veteran patients hospitalized between 1985 and 1990. The study followed 173,463 patients with diabetes and 650,620 without diabetes. No patient had acute or chronic liver disease recorded before, during, or within one year of their index hospitalization.

of patients with cirrhosis have overt diabetes and a larger percentage have impaired glucose tolerance. Thus, diabetes could be a result of cirrhosis.

Cohort studies, which are better suited to discern temporal relationships between exposure and disease, have been conducted that compared HCC incidence in cohorts of diabetic patients with either the expected incidence based on HCC rates in the underlying population or with the observed HCC incidence of a defined cohort without diabetes. Studies among diverse populations have reported that diabetes is associated with a 2 to 3-fold increased risk of HCC (Figure 7) (El-Serag et al. 2004), with a significantly greater relative risk among men than women (Hui Zhang et al. 2013). Longer duration of diabetes may be also associated with an incremental increase in risk of HCC; however, the relationship between diabetes severity or glycemic control and HCC risk is unclear (Lauby-Secretan et al. 2016). Several meta-analyses reported that treatment of type 2 diabetes with metformin decreases risk by as much as 50%, whereas use of insulin and sulfonylureas increases risk (Franciosi et al. 2013; Singh et al. 2013; Hui; Zhang et al. 2013). However, these studies could be confounded by diabetes severity. Patients with well controlled diabetes on metformin monotherapy could be a phenotypically different subset of patients with diabetes compared with patients who need insulin, thus the correlation of medication with disease severity might lead to an overestimation of risk reduction by metformin (Gordon et al. 2014).

Tobacco

The relationship between cigarette smoking and HCC has been examined in more than 50 studies in both low- and high-rate areas. In almost all countries, there were findings of both positive associations and lack of association. A 2014 US Surgeon General's report of 113 studies found a 70% increased risk of HCC in current smokers and 40% in former smokers (Alberg et al. 2014) compared to lifetime non-smokers. More recent data found that HCC risk returned to the non-smoker baseline 30 years after tobacco cessation (Petrick et al. 2018).

Coffee

Coffee has been consistently associated with decreased risk of liver cancer (Ma et al. 2019). A 2017 meta-analysis of both cohort and case-control studies reported that an extra two cups of coffee per day compared to no coffee was associated with a 35% reduced risk (Kennedy et al. 2017). Coffee has also been associated with lower liver enzyme levels, slower progression of fibrosis, and lower risk of diabetes. The mechanisms underlying a possible protective effect of coffee, however, are not clear. Experimental evidence suggests there may be beneficial effects of caffeine as well as many other coffee components (e.g., diterpenes) in reducing inflammation, fibrosis, insulin resistance and oncogenesis (H. I. Yang et al. 2011).

Genetic Epidemiology of HCC

Epidemiologic research has demonstrated that most adult-onset HCC cases are sporadic (i.e., have no similarly affected first-degree relative) and many have at least one established acquired (non-genetic) risk factor like habitual alcohol abuse or chronic infection with HBV or HCV. However, most people with these non-genetic risk factors for HCC never develop cirrhosis or HCC, and a sizable minority of HCC cases develop among individuals without any known risk factors. Few HCC cases are associated with familial disorders with mendelian inheritance like hereditary hemochromatosis, alpha-1-antitrypsin deficiency, or porphyria. Polymorphisms, originally examined in candidate-locus studies, have also been related to HCC risk. A 2011 meta-analysis found that polymorphisms in

UGT1A7, MnSOD and IL-1B were significantly associated with risk (Lee et al. 2018).

Genome-wide association studies (GWAS) conducted in Asian populations where HBV or HCV were factors reported increased risks in association with a number of loci, most commonly ones located in the HLA region (HLA-DP, HLA-DQ, HLA-DR, MICA) (Baecker et al. 2018; Jiang et al. 2013; Kumar et al. 2011; Lee et al. 2018; S. Li et al. 2012; Y., 2018; Y. Y. Lin et al. 2017; Maucort-Boulch et al. 2018; Miki et al. 2011; Qu et al. 2016; Hongxing Zhang et al. 2010). Another reported association maps to chromosome 1p36.22, a region that may harbor a tumor suppressor gene for HCC (Hongxing Zhang et al. 2010). The KIF1B gene in this region has been reported to be associated with apoptosis, and its association with HCC was replicated in subsequent studies from other Asian populations. Associations with STAT4, GRIK1, EFCAB11, and EFCAB11 have also been found (Y. Y. Lin et al. 2017; Miki et al. 2011; Hongxing Zhang et al. 2010). GWASs in Chinese and Japanese populations identified SNPs at chromosomes 1p36.22 (KIF1B), (B. Yang et al. 2017) 2q32.2-2q32.3 (STAT4) (Campbell et al. 2016), 6p21.3 (HLA-DQ) (Campbell et al. 2016), 6p21.32 (HLA-DQAQ/DRB1) (Florio et al. 2020), 6p21.33 (MICA) (Schlesinger et al. 2013), 7q21.13 (CDK14) (Stepanova et al. 2013), (52) 21q21.3 (GRIK1) (Florio et al. 2020), and 22q11.2 (DEPDC5) (Wattacheril and Chalasani 2012) as associated with HCC progression in patients with HBV or HCV infection.

Recent large GWAS have identified SNPs influencing the development and severity of NAFLD (Palmer et al. 2013). The strongest and most consistent associations are with rs738409 C>G SNP (I148M) of Patatin-like phospholipase domain-containing 3 (*PNPLA3*), and the variant risk allele was more prevalent in Hispanics than Europeans or African Americans (Ahmed et al. 2015). The rs738409 SNP in the *PNPLA3* gene was initially reported to be related to NAFLD (Romeo et al. 2008). A meta-analysis of studies of this polymorphism and risk of HCC found a significant association between this SNP and HCC among white populations (odds ratio = 1.75) but no evidence of an association among Asian populations (Z. Huang et al. 2019). Other variants with possible HCC associations include the rs58542926 C>T SNP (E167K) in transmembrane 6 superfamily 2 (*TM6SF2*) and the rs641738 C>T SNP of membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7*). A meta-analysis associated rs2228603 in Neurocan (*NCAN*) and rs4240624 in Protein Phosphatase 1 Regulatory Subunit 3B (*PPP1R3B*) with increased hep148Iatic steatosis in African Americans; the former had a reverse, protective effect in Hispanics (Vernon et al. 2011). A few studies have also demonstrated potential utility of a polygenic risk score derived from these NAFLD-related SNPs for predicting HCC in cured HCV (Degasperi et al. 2020; Wong et al. 2014) and NAFLD patients (Bianco et al. 2021; Kanwal et al. 2018).

Key Take Home Messages

- There has been a shift in the main HCC risk factors from strong but relatively infrequent agents (e.g., HBV and HCV) to weak but very common conditions (e.g., obesity, diabetes, metabolic syndrome).
- There has been a decline in the incidence of HBV and HCV (i.e., vaccination, screening of blood products), prevalence of HCV (i.e., effective novel HCC therapies), and carcinogenic potential of HCV (i.e., treatment related sustained virological response) and HBV (i.e., treatment related adequate viral suppression).
- HBV remains an important etiological especially in Asia and Africa.
- Novel highly effective therapies for HCV is expected to lead to further decline in rates of HCC in low HCC incidence countries like the US. However, despite HCV treatment, HCC risk remains elevated in those who already developed cirrhosis and hence HCC screening may still be needed in this group.
- Obesity, diabetes, and metabolic syndrome traits are associated with 1.5–2.0-fold increase in HCC that while mostly affects those with cirrhosis is increasingly recognized in patients without cirrhosis or advanced fibrosis.
- Host genetic variants (e.g., PNPLA3) and environmental risk factors (e.g., alcohol, aflatoxins, tobacco) are important HCC risk enhancers.

Knowledge Gaps

- The major shift of HCC risk factors toward common conditions (e.g., NAFLD, obesity, diabetes) creates major clinical and public health dilemmas, and requires examination and identification of demographic, clinical, genetic, and biochemical markers of HCC that allows better risk stratification and relatively targeted prevention and screening strategies.
- The increasing number of people with treated HCV and HBV need to be examined to determine the residual risk of HCC and the determinants of this risk.
- The considerable disparities in HCC incidence among racial and ethnic groups, and the possible role of socioeconomic determinants of health needs to examined.
- The potential clinical role of host genetics (e.g., polygenic risk scores) as predictors of the incidence and prognosis of HCC needs to be examined.

Trusted Websites for Further Reading

- https://www.mayoclinic.org/diseases-conditions/hepatocellular-carcinoma/cdc-20354552
- https://www.mdanderson.org/cancerwise/giving-others-hope-after-hepatocellular-carcinoma.h00-158986656.html

References

Adams, L.A., Lymp, J.F., St. Sauver, J. et al. (2005). The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* doi: 10.1053/j.gastro.2005.04.014.

Ahmed, A., Wong, R.J., and Harrison, S.A. (2015). Nonalcoholic Fatty Liver Disease Review: diagnosis, Treatment, and Outcomes. *Clin Gastroenterol Hepatol* doi: 10.1016/j.cgh.2015.07.029.

Alberg, A.J., Shopland, D.R., and Cummings, K.M. (2014). The 2014 Surgeon general's report: commemorating the 50th Anniversary of the 1964 Report of the advisory committee to the US Surgeon general and updating the evidence on the health consequences of cigarette smoking. *Am J Epidemiol* doi: 10.1093/aje/kwt335.

Armstrong, G.L., Alter, M.J., McQuillan, G.M., and Margolis, H.S. (2000). The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* (Baltimore, Md) 31 (3): 777–782. doi: 10.1002/hep.510310332.

Baecker, A., Liu, X., La Vecchia, C., and Zhang, Z.F. (2018). Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. *Eur J Cancer Prev* doi: 10.1097/CEJ.0000000000000428.

Berentzen, T.L., Gamborg, M., Holst, C. et al. (2014). Body mass index in childhood and adult risk of primary liver cancer. *J Hepatol* doi: 10.1016/j.jhep.2013.09.015.

Bianco, C., Jamialahmadi, O., Pelusi, S. et al. (2021). Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. *J Hepatol* doi: 10.1016/j.jhep.2020.11.024.

Bray, F., Colombet, M., Mery, L. et al. (2017). *Cancer Incidence in Five Continents*, vol. XI. electronic version Lyon: In International Agency for Research on Cancer.

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer J Clin* 68 (6): 394–424. doi: 10.3322/caac.21492.

Bressac, B., Kew, M., Wands, J., and Ozturk, M. (1991). Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. *Nature* doi: 10.1038/350429a0.

Campbell, P.T., Newton, C.C., Freedman, N.D. et al. (2016). Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. adults. *Cancer Res* doi: 10.1158/0008-5472.CAN-16-0787.

Cheemerla, S. and Balakrishnan, M. (2021). Global epidemiology of chronic liver disease. *Clin Liver Dis* 17 (5): 365–370. doi: 10.1002/cld.1061.

Chen, J.G., Egner, P.A., Ng, D. et al. (2013). Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. *Cancer Prev Res* doi: 10.1158/1940-6207.CAPR-13-0168.

Davila, J.A. (2005). Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 54 (4): 533–539. doi: 10.1136/gut.2004.052167.

Davis, G.L., Alter, M.J., El-Serag, H. et al. (2010). Aging of Hepatitis C Virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* doi: 10.1053/j.gastro.2009.09.067.

Degasperi, E., Galmozzi, E., Pelusi, S. et al. (2020). Hepatic fat—Genetic risk score predicts hepatocellular carcinoma in patients with cirrhotic HCV treated with DAAs. *Hepatology* doi: 10.1002/hep.31500.

Donato, F., Tagger, A., Gelatti, U. et al. (2002). Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* doi: 10.1093/aje/155.4.323.

El-Serag, H.B. (2012). Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* doi: 10.1053/j.gastro.2011.12.061.

El-Serag, H.B. and Kanwal, F. (2014). Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology* doi: 10.1002/hep.27222.

El-Serag, H.B. and Rudolph, K.L. (2007). Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 132 (7): 2557–2576. doi: 10.1053/j.gastro.2007.04.061.

El-serag, H.B., Tran, T., and Everhart, J.E. (2004). Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 126 (2): 460–468. doi: 10.1053/j.gastro.2003.10.065. PMID: 14762783.

Fasani, P., Sangiovanni, A., De Fazio, C. et al. (1999). High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. *Hepatology* doi: 10.1002/hep.510290604.

Florio, A.A., Campbell, P.T., Zhang, X. et al. (2020). Abdominal and gluteofemoral size and risk of liver cancer: the liver cancer pooling project. *Int J Cancer* doi: 10.1002/ijc.32760.

Franciosi, M., Lucisano, G., Lapice, E. et al. (2013). Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. *PLoS ONE* doi: 10.1371/journal.pone.0071583.

Frezza, M., di Padova, C., Pozzato, G. et al. (1990). High blood alcohol levels in women. *New Engl J Med* doi: 10.1056/nejm199001113220205.

Frezza, M., Padova, C., di Pozzato, G. et al. (1992). High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *Ann Rev Add Res Treat* doi: 10.1056/NEJM199001113220205.

Garner, R.C., Miller, E.C., and Miller, J.A. (1972). Liver microsomal metabolism of aflatoxin B 1 to a reactive derivative toxic to Salmonella typhimurium TA 1530. *Cancer Res.* 32 (10): 2058–66. PMID: 4404160.

Gordon, S.C., Lamerato, L.E., Rupp, L.B. et al. (2014). Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. *Clin Gastroenterol Hepatol* doi: 10.1016/j.cgh.2013.09.062.

Hagström, H., Tynelius, P., and Rasmussen, F. (2018). High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: a national, population-based cohort study in 1.2 million men. *Gut* doi: 10.1136/gutjnl-2016-313622.

Huang, D.Q., El-Serag, H.B., and Loomba, R. (2021). Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 18 (4): 223–238. doi: 10.1038/s41575-020-00381-6.

Huang, X. and Hollinger, F.B. (2014). Occult hepatitis B virus infection and hepatocellular carcinoma: a systematic review. *J Viral Hepat* 21 (3): 153–162. doi: 10.1111/jvh.12222.

Huang, Z., Guo, X., Zhang, G. et al. (2019). Correlation between PNPLA3 rs738409 polymorphism and hepatocellular carcinoma: a meta-analysis of 10,330 subjects. *Int J Biol Mark* doi: 10.1177/1724600818812471.

Ioannou, G.N., Green, P.K., and Berry, K. (2017). HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol* doi: 10.1016/j.jhep.2017.08.030.

Jiang, D.K., Sun, J., Cao, G. et al. (2013). Genetic variants in STAT4 and HLA-DQ genes confer risk of hepatitis B virus-related hepatocellular carcinoma. *Nat Gen* doi: 10.1038/ng.2483.

Kanwal, F., Kramer, J.R., Mapakshi, S. et al. (2018). Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 155 (6): 1828–1837.e2. doi: 10.1053/j.gastro.2018.08.024.

Kawamura, Y., Arase, Y., Ikeda, K. et al. (2012). Large-scale long-term follow-up study of Japanese patients with non-alcoholic fatty liver disease for the onset of hepatocellular carcinoma. *Am J Gastroenterol* doi: 10.1038/ajg.2011.327.

Kennedy, O.J., Roderick, P., Buchanan, R. et al. (2017). Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open* 7 (5): e013739. doi: 10.1136/bmjopen-2016-013739.

Kim, H.S. and El-Serag, H.B. (2019). The epidemiology of hepatocellular carcinoma in the USA. *Curr Gastroenterol Rep* doi: 10.1007/s11894-019-0681-x.

Kulik, L. and El-Serag, H.B. (2019). Epidemiology and management of hepatocellular carcinoma. *Gastroenterology* 156 (2): 477–491.e1. doi: 10.1053/j.gastro.2018.08.065.

Kumar, V., Kato, N., Urabe, Y. et al. (2011). Genome-wide association study identifies a susceptibility locus for HCV-induced hepatocellular carcinoma. *Nat Gen* doi: 10.1038/ng.809.

La Vecchia, C., Negri, E., Decarli, A., and Franceschi, S. (1997). Diabetes mellitus and the risk of primary liver cancer. *Int J Cancer* 73 (2): 204–207. http://www.ncbi.nlm.nih.gov/pubmed/9335443.

Lauby-Secretan, B., Scoccianti, C., Loomis, D. et al. International Agency for Research on Cancer Handbook Working Group. (2016). Body fatness and cancer–Viewpoint of the IARC working group. *New Engl J Med* 375 (8): 794–798. doi: 10.1056/NEJMsr1606602.

Lee, M.H., Huang, Y.H., Chen, H.Y. et al. (2018). Human leukocyte antigen variants and risk of hepatocellular carcinoma modified by hepatitis C virus genotypes: a genome-wide association study. *Hepatology* doi: 10.1002/hep.29531.

Li, S., Qian, J., Yang, Y. et al. (2012). GWAS identifies novel susceptibility loci on 6p21.32 and 21q21.3 for hepatocellular carcinoma in chronic hepatitis B virus carriers. *PLoS Genet* doi: 10.1371/journal.pgen.1002791.

Li, Y., Zhai, Y., Song, Q. et al. (2018). Genome-Wide association study identifies a new locus at 7q21.13 associated with hepatitis b virus–Related hepatocellular carcinoma. *Clin Cancer Res*. doi: 10.1158/1078-0432.CCR-17-2537.

Lin, C.-L. and Kao, J.-H. (2020). Hepatitis B: immunization and impact on natural history and cancer incidence. *Gastroenterol Clin North Am* 49 (2): 201–214. doi: 10.1016/j.gtc.2020.01.010.

Lin, Y.Y., Yu, M.W., Lin, S.M. et al. (2017). Genome-wide association analysis identifies a GLUL haplotype for familial hepatitis B virus-related hepatocellular carcinoma. *Cancer* doi: 10.1002/cncr.30851.

Liu, Y., Chang, C.C.H., Marsh, G.M., and Wu, F. (2012). Population attributable risk of aflatoxin-related liver cancer: systematic review and meta-analysis. *Eur J Cancer* doi: 10.1016/j.ejca.2012.02.009.

Ma, Y., Yang, W., Li, T. et al. (2019). Meat intake and risk of hepatocellular carcinoma in two large US prospective cohorts of women and men. *Int J Epidemiol* doi: 10.1093/ije/dyz146.

Marrero, J.A., Kulik, L.M., Sirlin, C.B. et al. (2018). Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. *Hepatology* doi: 10.1002/hep.29913.

Maucort-Boulch, D., de Martel, C., Franceschi, S., and Plummer, M. (2018). Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer* doi: 10.1002/ijc.31280.

McGlynn, K.A., Petrick, J.L., and El-Serag, H.B. (2021). Epidemiology of hepatocellular carcinoma. *Hepatology* (Baltimore, Md) 73 (Suppl 1): 4–13. doi: 10.1002/hep.31288.

McGlynn, K.A., Petrick, J.L., and London, W.T. (2015). Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis* 19 (2): 223–238. doi: 10.1016/j.cld.2015.01.001.

Miki, D., Ochi, H., Hayes, C.N. et al. (2011). Variation in the DEPDC5 locus is associated with progression to hepatocellular carcinoma in chronic hepatitis C virus carriers. *Nat Gen* doi: 10.1038/ng.876.

Mittal, S., El-Serag, H.B., Sada, Y.H. et al. (2016). Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 14 (1): 124–131.e1. doi: 10.1016/j.cgh.2015.07.019.

Mohammadian, M., Allah Bakeshei, K., and Mohammadian-Hafshejani, A. (2020). International epidemiology of liver cancer: geographical distribution, secular trends and predicting the future. *J Prev Med Hyg* 61 (2): E259–E289. doi: 10.15167/2421-4248/jpmh2020.61.2.1244.

Morgan, R.L., Baack, B., Smith, B.D. et al. (2013). Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Internal Med* doi: 10.7326/0003-4819-158-5-201303050-00005.

Ohkuma, T., Peters, S.A.E., and Woodward, M. (2018). Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. *Diabetologia* doi: 10.1007/s00125-018-4664-5.

Okuda, K., Nakanuma, Y., and Miyazaki, M. (2002). Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. *J Gastroenterol Hepatol* 17 (10): 1049–1055. doi: 10.1046/j.1440-1746.2002.02781.x.

Orci, L.A., Sanduzzi-Zamparelli, M., Caballol, B. et al. (2021). Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Clin Gastroenterol Hepatol* doi: 10.1016/j.cgh.2021.05.002.

Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42 (1987). IARC monographs on the evaluation of carcinogenic risks to humans. *Supplement* 7: 1–440. http://www.ncbi.nlm.nih.gov/pubmed/3482203.

Palmer, N.D., Musani, S.K., Yerges-Armstrong, L.M. et al. (2013). Characterization of European ancestry nonalcoholic fatty liver disease-associated variants in individuals of African and Hispanic descent. *Hepatology* doi: 10.1002/hep.26440.

Papatheodoridis, G.V., Lampertico, P., Manolakopoulos, S., and Lok, A. (2010). Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* doi: 10.1016/j.jhep.2010.02.035.

Park, H., Shin, S.K., Joo, I. et al. (2020). Systematic review with meta-analysis: low-level alcohol consumption and the risk of liver cancer. *Gut and Liver* 14 (6): 792–807. doi: 10.5009/gnl19163.

Petrick, J.L., Campbell, P.T., Koshiol, J. et al. (2018). Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the liver cancer pooling project. *Br J Cancer* doi: 10.1038/s41416-018-0007-z.

Petrick, J.L., Florio, A.A., Znaor, A. et al. (2020). International trends in hepatocellular carcinoma incidence, 1978–2012. *Int J Cancer* doi: 10.1002/ijc.32723.

Petrick, J.L., Kelly, S.P., Altekruse, S.F. et al. (2016). Future of hepatocellular carcinoma incidence in the United States forecast through 2030. *J Clin Oncol* doi: 10.1200/JCO.2015.64.7412.

Petrick, J.L. and McGlynn, K.A. (2019). The changing epidemiology of primary liver cancer. *Curr Epidemiol Rep* 6 (2): 104–111. doi: 10.1007/s40471-019-00188-3.

Qu, L.S., Jin, F., Guo, Y.M. et al. (2016). Nine susceptibility loci for hepatitis B virus-related hepatocellular carcinoma identified by a pilot two-stage genome-wide association study. *Oncol Lett* doi: 10.3892/ol.2015.3958.

Romeo, S., Kozlitina, J., Xing, C. et al. (2008). Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Gen* doi: 10.1038/ng.257.

Sangaramoorthy, M., Yang, J., DeRouen, M.C. et al. (2020). Disparities in hepatocellular carcinoma incidence in California: an update. *Cancer Epidemiol, Biomark Prev: A Publication Am Ass Cancer Res, Cosponsored Am Soc Prev Oncol* 29 (1): 79–87. doi: 10.1158/1055-9965.EPI-19-0560.

Schlesinger, S., Aleksandrova, K., Pischon, T. et al. (2013). Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. *Int J Cancer* doi: 10.1002/ijc.27645.

Sharma, R. (2020). Descriptive epidemiology of incidence and mortality of primary liver cancer in 185 countries: evidence from GLOBOCAN 2018. *Jpn J Clin Oncol* 50 (12): 1370–1379. doi: 10.1093/jjco/hyaa130.

Singh, S., Singh, P.P., Singh, A.G. et al. (2013). Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 108 (6): 881–891. quiz 892. doi: 10.1038/ajg.2013.5.

Sorensen, H.T., Friis, S., Olsen, J.H. et al. (1998). Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology* (Baltimore, Md) 28 (4): 921–925. doi: 10.1002/hep.510280404.

Stepanova, M., Rafiq, N., Makhlouf, H. et al. (2013). Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci* 58 (10): 3017–3023. doi: 10.1007/s10620-013-2743-5.

Stroffolini, T., Andreone, P., Andriulli, A. et al. (1999). Gross pathologic types of hepatocellular carcinoma in Italy. *Oncology* doi: 10.1159/000011963.

Sun, Z., Chen, T., Thorgeirsson, S.S. et al. (2013). Dramatic reduction of liver cancer incidence in young adults: 28 Year follow-up of etiological interventions in an endemic area of China. *Carcinogenesis* doi: 10.1093/carcin/bgt007.

Tseng, C.H., Tseng, C.M., Wu, J.L. et al. (2020). Magnitude of and prediction for risk of hepatocellular carcinoma in patients with chronic hepatitis B taking entecavir or tenofovir therapy: a systematic review. *J Gastroenterol Hepatol (Australia)* doi: 10.1111/jgh.15078.

Turati, F., Galeone, C., Rota, M. et al. (2014). Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Ann Oncol* doi: 10.1093/annonc/mdu020.

Turner, P.C., Sylla, A., Diallo, M.S. et al. (2002). The role of aflatoxins and hepatitis viruses in the etiopathogenesis of hepatocellular carcinoma: a basis for primary prevention in Guinea-Conakry, West Africa. *J Gastroenterol Hepatol (Australia)* doi: 10.1046/j.1440-1746.17.s4.7.x.

Udomkun, P., Wiredu, A.N., Nagle, M. et al. (2017). Innovative technologies to manage aflatoxins in foods and feeds and the profitability of application – a review. *Food Control* doi: 10.1016/j.foodcont.2017.01.008.

Valery, P.C., Laversanne, M., Clark, P.J. et al. (2018). Projections of primary liver cancer to 2030 in 30 countries worldwide. *Hepatology* (Baltimore, Md) 67 (2): 600–611. doi: 10.1002/hep.29498.

Vernon, G., Baranova, A., and Younossi, Z.M. (2011). Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Alimentary Pharmacology and Therapeutics* 34 (Issue 3): 274–285. doi: 10.1111/j.1365-2036.2011.04724.x.

Wattacheril, J. and Chalasani, N. (2012). Nonalcoholic fatty liver disease (NAFLD): is it really a serious condition? *Hepatology* doi: 10.1002/hep.26031.

White, D.L., Kanwal, F., and El-Serag, H.B. (2012). Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol: Off Clin Pract J Am Gastroenterol Ass* 10 (12): 1342–1359.e2. doi: 10.1016/j.cgh.2012.10.001.

Wong, R.J., Cheung, R., and Ahmed, A. (2014). Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology* doi: 10.1002/hep.26986.

World Health Organization (2015). World health organisation. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva. World Health Organisation. In *WHO*.

Yang, B., Petrick, J.L., Kelly, S.P. et al. (2017). Adiposity across the adult life course and incidence of primary liver cancer: the NIH-AARP cohort. *Int J Cancer* doi: 10.1002/ijc.30737.

Yang, H.I., Yuen, M.F., Chan, H.L.Y. et al. (2011). Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* doi: 10.1016/S1470-2045(11)70077-8.

Yoshizawa, H. (2002). Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 62 (Suppl 1): 8–17. doi: 10.1159/000048270.

Younossi, Z.M. and Henry, L. (2021). Epidemiology of non-alcoholic fatty liver disease and hepatocellular carcinoma. *JHEP Rep* doi: 10.1016/j.jhepr.2021.100305.

Yu, S.Z. (n.d.). Primary prevention of hepatocellular carcinoma. *J Gastroenterol Hepatol* 10 (6): 674–682. doi: 10.1111/j.1440-1746.1995.tb01370.x.

Zhang, H., Zhai, Y., Hu, Z. et al. (2010). Genome-wide association study identifies 1p36.22 as a new susceptibility locus for hepatocellular carcinoma in chronic hepatitis B virus carriers. *Nat Gen* doi: 10.1038/ng.638.

Zhang, H., Gao, C., Fang, L. et al. (2013). Metformin and reduced risk of hepatocellular carcinoma in diabetic patients: a meta-analysis. *Scand J Gastroenterol* doi: 10.3109/00365521.2012.719926.

Zhang, X., El-Serag, H.B., and Thrift, A.P. (2020). Sex and race disparities in the incidence of hepatocellular carcinoma in the United States examined through age–period–cohort analysis. *Cancer Epidemiol Biomark Prev* doi: 10.1158/1055-9965.EPI-19-1052.

15 Pathology, Molecular Pathology, and Genomics of Hepatobiliary and Pancreatic Cancer

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Hepatic Cancer

Hepatocellular carcinoma (HCC) is a primary malignant tumor of the liver consisting of epithelial cells displaying hepatocellular differentiation. On histological grounds the proliferating cells usually form trabeculae or macrotrabeculae as well as pseudoglands and solid nests with obliteration of normal hepatic architecture including portal tracts and reticulin framework loss, arterialization, and capillarization. Based on H&E staining, histological grading is performed by comparison of the cancer cells (nuclear atypia and cytoplasm) to nonneoplastic hepatocytes and divide hepatocellular carcinoma into three degrees of differentiation: well differentiated, moderately differentiated, and poorly differentiated (Burt et al. 2018; Han et al. 2013). As in many cases there might be more than one grade and it is always the worst which predicts the prognosis (Han et al. 2013). For establishing hepatocellular origin and differentiating liver tumors from premalignant and nonneoplastic changes, several immunohistochemical markers can be utilized as well as diagnostic molecular pathology methods. The most widely used hepatocellular markers are Arginase-1, HepPar 1, HSP70, glutamine synthetase (GS), Glypican 3, polyclonal CEA, CD10 and AFP however none of these markers is sensitive enough to base the diagnosis on and has to be considered in conjunction with histological picture since the expression differs between tumor grade and subtype. In reference to molecular profile the most common gene mutations in HCC include *TERT* promoter, *TP53*, *CTNNB1*, *AXIN1*, *ARID1A*, *ARID1B*, *ARID2*, *FGF19* amplification, DNA methylation and amplification (Schulze et al. 2015; Nault et al. 2014;).

According to WHO 2019 classification the special subtype can be determined in 35% of HCCs and is related to histoclinical picture, molecular profile, prognosis, and therapeutical approach (WHO 2019). These special subtypes include:

The subtypes with the worse prognosis:

- Macrotrabecular massive pattern (MTM) HCC with the incidence of 5% developing in patients with HBV infection. Histologically it is characterized by the presence of thick cord (up to 10 cells) of neoplastic cells and vascular invasion. Molecularly *TP53* mutations and *FGF19* amplifications are common as is activation of angiogenesis (high ANGPT2 mRNA levels) (Calderaro et al. 2017).
- Neutrophil rich HCC with low incidence (1%) and neutrophil rich inflammatory infiltrate within neoplastic cells and focal sarcomatoid appearance. The patients have elevated numbers of WBC and increased concentration of CRP and IL6 in the serum while the tumor produces G-CSF which can be displayed immunohistochemically (Torbenson 2017).
- Scirrhous HCC in 4% of cases in which >50% of area is occupied by intratumoral fibrosis, the activation of EMT and TGFβ signaling pathways and TSC1/TSC2 mutations are present (Seok et al. 2012; WHO 2019).

The subtypes with the similar prognosis (to not the "specified type" of HCC)

- Steatohepatic HCC with the incidence of 5–20% in patients with metabolic syndrome or alcohol abuse. Histologically is characterized by the presence of inflammatory cells in the context of steatosis (steatohepatitis) in >50% of the tumor. The activation of the Il-6/JAK/STAT pathway is often present with lower frequency of *TERT*, *CTNNB1* and *TP53* mutations (Calderaro et al. 2017).
- Fibrolamellar HCC comprises 1% of the cases and occur in younger patients in noncirrhotic liver. Microscopically large eosinophilic cells with prominent nucleoli are seen mixed with dense, lamellar fibrosis. The molecular hallmark of lamellar HCC is DNAJB1-PRKACA gene fusion with subsequent protein kinase A activation. This fusion can be detected in FISH assay (Graham and Torbenson 2017).
- Chromophobe HCC with the 3% incidence rate and partly clear (chromophobe) cytoplasm and blunt nuclei in histology. Alternative lengthening of telomere is a key molecular feature of this subtype (Torbensosn 2017).

The subtypes with better prognosis:

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- Lymphocyte-rich HCC with low (<1%) incidence rate and rich lymphocyte (CD8+) infiltrate outnumbering the tumor cells and forming lymphocyte-rich HCC (with well or moderately differentiated cancer cells) or lymphoepithelioma-like HCC (with poorly differentiated cancer cells). No specific molecular changes responsible for its development are found up to date and EBV infection seems to be not related to this subtype (Torbensosn 2017; Wada et al. 1998).
- Clear cell HCC occurring in 3–7% of patients where the clear cell change (due to glycogen accumulation) is found in more than 80% cells of the tumor. No molecular basis has been established in this subtypes but the tumors are usually less advanced with better differentiation and no lymphovascular invasion which warrants better prognosis (Li et al. 2011).

This histological subtypes with their clinical characteristics and gene mutations make the proposal to molecular tumor classification which may be adopted to clinical practice in the future (Calderaro et al. 2017).

In 4–28% of HCC the expression of CK19 is positive. It is a marker of cholangiocytes and liver progenitor cells and signifies the worse prognosis in HCC patients. Clinically these patients have higher levels of AFP, cancer is often related to HBV infection and is more advanced with lymph node metastases. On pathological level the type of growth is infiltrative with abundant fibrotic stroma and frequent vascular invasion (Rhee 2020). Furthermore, in these cases the TGFβ and EMT pathways are activated and the tumors are resistant to TACE and RFA therapies. (Rhee 2020).

WHO (2019) classification settles the concept of combined hepatocellular and cholangiocellular carcinoma (cHCC-CCA) as a tumor with unequivocal differentiation toward hepatic and cholangiocytic cells within the same tumor. The diagnosis is based only on H&E histological picture and IHC is used as adjunct methods with HepPar1, ARG1, Gly3, pCEA, CD10, AFP in favor of HCC and CK7, CK19, and EpCAM in favor of CCA (Siarra 2020). Based on international consensus proposed by Burt E and al (Burt et al. 2018) stem cell/progenitor and intermediate cell subtypes as well as cholangiolocelluar carcinoma (CLC) with HCC (WHO 2010) have been removed and placed under cHCC-CCA umbrella (usually representing part or foci of histological pattern) whereas the CLC without HCC has been incorporated into the CCA group as a subtype (Moeini et al. 2017). The term intermediate cell carcinoma is preserved for the rare cases where the nearly entire tumor is composed of monotonous cells with scant cytoplasm with the morphology in between hepatocytes and cholangiocytes embedded in rich fibrous stroma.

Cholangiocarcinomas

Cholangiocarcinomas are the epithelial tumors arising anywhere along biliary tree and are anatomically divided into intrahepatic cholangiocarcinomas (iCCAs) which arise proximal to the second order bile ducts, perihilar cholangiocarcinomas (pCCAs) which arise between second order biliary ducts and cystic duct and distal extrahepatic cholangiocarcinoma (dCCAs) which arise between cystic duct and the ampulla of Vater (Labib et al. 2019; Rizvi et al. 2017). These tumors are also classified based on their macroscopic appearance (mass-forming, periductal, or intraductal) or the cell of origin (cholangicytes, peribilliary glands, hepatic progenitor cells, or hepatocytes (Labib et al. 2019). Most of cholangiocarcinomas are adenocarcinomas consisting of variably sized and shaped glands built of variably atypical columnar or cuboidal neoplastic cells with conspicuous pale cytoplasm surrounded typically by rather rich fibrotic stroma. There are significant differences between types of cholangiocarcinoma in terms of histology, immunophenotype, and molecular characteristics.

iCCA consists of two main types: large duct and small duct iCCA. The former arises in large intrahepatic bile ducts close to the liver hilum and the latter develops peripherally within liver parenchyma. Morphologically large duct type iCCA resembles distal cholangiocarcinomas (pCCAs and dCCAs) and is characterized by large ducts lined by columnar epithelium producing mucus. These glands are embedded in rich fibrous stroma (Figure 1). The presence of neural and lymphovascular invasion is typical as is the presence of lymph nodes metastases. The small duct type iCCA is formed by small tubules with variably sized lumens lined by small cuboidal cells with less pronounced production of mucus and ductular and cord-like components with slit-like lumina. The cancer replaces liver parenchyma and the rich fibrous stroma is also the feature. For large duct type iCCA it is believed to be biliary intraepithelial neoplasia (BillN) to be

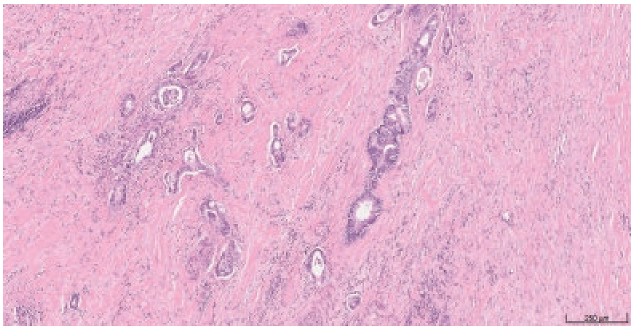

Figure 1 Cholangiocarcinoma large duct type, H&E x6,3.

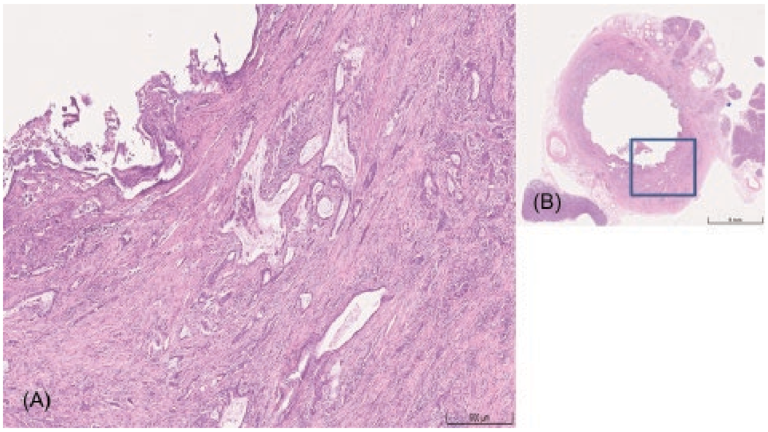

Figure 2 Adenocarcinoma of ductus choledochus, H&E Ax0,2, Bx3,1.

the microscopic precursor lesion whereas the cell of origin for small duct type iCCA is still debated. The distinction between large duct and small duct type iCCA may be challenging especially in tumors with mixed histology, in poorly differentiated tumors or in small biopsies. This requires additional immunohistochemical stainings and/or genetic tests proving the biliary origin of the tumor and differentiating between subtypes of iCCA. There are several common markers in biliary tree originated cancers including CK7, CK19, EMA (MUC1) but neither of them is entirely specific and should be always interpreted with histology. For establishing the diagnosis of small duct type iCCA the panel of N-cadherin, CD56 CRP and tubulin-beta3 (TUBB3) markers can be performed while S100P expression is supposed to be more specific for large duct type iCCA.

The genetic milieu of intrahepatic carcinoma may be subclassified into inflammation subtype with morphological cholangiolar differentiation and activation of inflammatory pathways that is, IL10 and IL6 overexpression and STAT3 activation and proliferation subtype with moderate/poor histological differentiation, chromosomal instability, and activation of oncogenes like *RAS, MAPK, c-MET, BRAF* and *KRAS* (Graham et al. 2014). It is in up to 40% cases of iCCAs that the main driver mutation can be determined (Braconi et al. 2019). Analyzing the molecular profile of iCCAs there are also significant differences between the subtypes. In large duct type iCCA the gene mutations are similar to more distal and pancreatic lesions with *KRAS, SMAD4, MDM2, ERBB2*, and *TP53* mutations or amplifications. The small duct type iCCA hosts different and more specific list of molecular changes including *IDH1/IDH2, ARID1A BAP1*, and *BRAF* mutations and *FGFR2* fusion which seems to be reserved to this subtype only (Akita et al. 2017; Saha et al. 2014). This warrants the rapidly evolving area of precisely directed antitumor treatment. The FGFR2 gene fusion is present in 10–20% of CCA and FGFR2 alterations can be detected by NGS, FISH or immunohistochemical methods (Maruki et al. 2021) for the selection of patients who might respond to FGFR competitive inhibitor. Similarly, frequent IDH1/2 mutated iCCAs may respond to specific inhibitor therapy and the status of the tumor can be determined by NGS. (Abou-Alfa et al. 2020).

It is to be underlined that histologic diagnosis of iCCA might be difficult in terms of differentiation with other adenocarcinomas metastasizing to the liver. As mentioned earlier, there is no specific immunohistochemical marker for iCCA and the metastatic tumors of certain origin may also produce rich fibrotic stroma and be neuroinvasive. The wide panel of IHC for exclusion should be then performed as proposed for cancer of unknown primary (CUP) (Fizazi et al. 2015). The thorough morphomolecular analysis methods though have shifted substantial number of cases from CUP to iCCA based on the specific genetic driver change.

The microscopic diagnosis of pCCAs and dCCAs is especially challenging due to shortage of material. Histologically these tumors are composed of blunt, often well differentiated cancer glands with sometimes minimal atypia and abundant cytoplasm. Cancer cells are embedded in rich fibrotic stroma and the type of growth may be mass forming or locally narrowing the bile ducts (Figure 2). The acquisition of histological material is sometimes impossible so the diagnoses must rely on cytology acquired during ERCP or EUS procedures. Conventional cytology is highly specific (97%) but has the sensitivity of only 43%. The specimens are often inadequate since CCAs are desmoplastic and paucicellular. The diagnostic performance may be improved by using additional methods on cytology material to prove neoplastic nature of the cells. FISH analyses to confirm the chromosomal instability (aneusomy or polysomy), NGS panels for driver mutations detection or miRNAs detection also in bile fluid (Rizvi et al. 2017).

Ductal Adenocarcinoma of Pancreas

Morphologically ductal adenocarcinoma is characterized by the formation of well or moderately differentiated glandular structures with luminar or intracellular mucin infiltrating pancreatic parenchyma and evoking strong desmoplastic reaction and production of rich fibrotic stroma (Figure 3). The amount of stroma, number of cancer associated fibroblasts, myofibroblasts, vessels, and inflammatory cells (lymphocytes and macrophages) may quite often be higher than neoplastic epithelial component. In well-differentiated adenocarcinomas the glands may be angular, branching, ruptured with multilayered epithelium and cribriform pattern while in moderately differentiated cases the tumor is more heterogenous and the well-differentiated component is intermixed with cribriform, papillary, micropapillary, and gyriform forming patterns as well as with the foci of more pleomorphic cells which takes place usually at the margin of the tumor. The cancer cells are cuboidal or columnar with round or ovoid nuclei. The nucleoli are inconspicuous, and the mitotic figures are rare. The cytoplasm is eosinophilic, foamy, or clear. Well-differentiated ductal adenocarcinoma is sometimes extremely difficult to distinguish from nonneoplastic ducts and the tumor specific histological features are of value in making microscopic diagnosis. Perineural invasion is quite specific for ductal adenocarcinoma as is lymphatic and vascular invasion (Figure 4). The neoplastic epithelium may completely replace the endothelium of the vein which resemble and may be mistaken for pancreatic intraepithelial neoplasia (PanIN). For highly suggestive of neoplastic nature should be treated the presence of isolated (naked ducts) glands in fatty tissue or in proximity of muscular arteries and unaccompanied vessels within or at the periphery of the lesion. Sometimes the neoplastic glands invade nonneoplastic acini or are intermingled with the remnants of islets or single islets cells (cancerization of the acini). The poorly differentiated ductal adenocarcinoma contains abundant sheets of solid or trabecular and cribriform neoplastic cells as well as individual cancer cells immersed in more loosely structured stroma (Shlitter et al. 2017). The production of the mucus is decreased, the cells are evidently pleomorphic with numerous mitoses and focal squamous or spindle cell metaplasia.

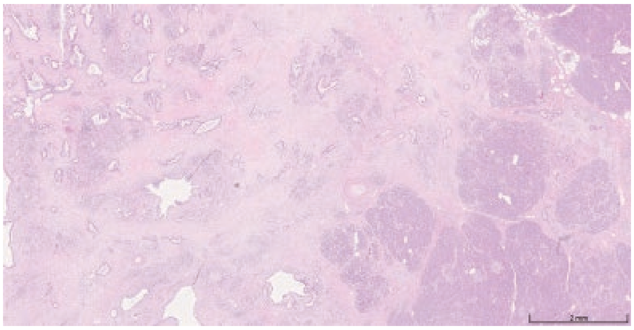

Figure 3 Ductal adenocarcinoma of the pancreas – classical type, H&E x1,3.

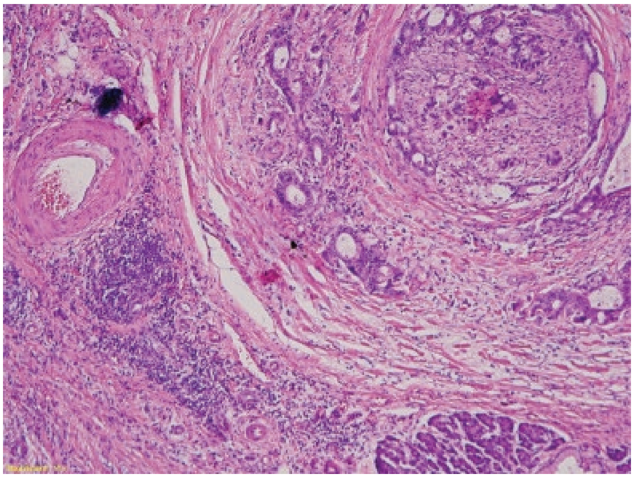

Figure 4 Adenocarcinoma of the pancreas – neuroinvasion, H&E x10.

The common immunohistochemical markers of ductal adenocarcinoma include CK7, CK8/18, CK19, CEA, Ca 19–9, EMA (MUC1), and MUC5AC but neither of them is sufficiently specific and sensitive for unequivocal confirmation and/or differentiation of ductal adenocarcinoma from other mucin producing adenocarcinomas particularly from bile ducts and the stomach. Ductal adenocarcinoma is usually negative for vimentin (expect for undifferentiated carcinoma), neuroendocrine markers (chromogranin A and synaptophysin) and acinar markers (BCL10, trypsin). The loss of nuclear expression of SMAD4(DPC4) and p16(CDKN2A) or the loss/gain of p53 expression can be observed in 55%, 75%, and 75–80% of cases respectively (Shiltter et al. 2017), which include the most prevalent mutations in ductal adenocarcinoma along with KRAS mutation. In addition, the ongoing studies on PDAC have divided this tumor molecularly into classical and basal-like types oncogenic pathways both with activated or normal stroma. Within the subtypes (squamous, ADEX, pancreatic progenitor, and immunogenic) there are lesions with different histology, prognosis, and potential therapeutic approach) (Bailey et al. 2016; Collisson et al. 2019).

There are several morphological patterns and histological subtypes of ductal adenocarcinoma that can be distinguished microscopically, differ immunohistochemically and molecularly, have different prognosis, and may require different therapeutical approach.

1 Morphological patterns:

Large duct pattern – neoplastic duct measure >0.5 mm and are very well differentiated and blunt and have to be differentiated form intraductal papillary mucionous neoplasm (IPMN) (Kosmahl et al. 2005).

Ductal adenocarcinoma with foamy gland pattern – neoplastic glands with foamy or vacuolated cytoplasm with basally located nuclei of gastric like foveolar epithelium type, very well differentiated, requires differentiation form non neoplastic epithelium (Dursun et al. 2010).

2 Histological subtypes:

Adenosquamous carcinoma – ductal carcinoma with squamous differentiation recognized when the squamous component exceeds 30% of the tumor (Borazanci et al. 2015). The squamous part of the tumor should display squamous epithelium markers (p63, p40) and these tumors almost universally harbor KRAS mutations in codon 12 (367), TP53, p16(CDKN2A) and SMAD4 mutations. They belong to the basal-like genomic subtype of ductal adenocarcinoma and warrants worse prognosis (Bailey et al. 2016) (Figure 5).

Colloid carcinoma – consist of neoplastic epithelium suspended in extracellular mucin pools. This lesion arises from intestinal type IPMN and the cells express intestinal markers (CDX2 and MUC2). Colloid carcinoma is supposed to have better prognosis than common type PDAC.

Medullary carcinoma – is characterized by the syncytial growth of epithelial cells with occasional glandular formations which are intermixed and surrounded by dense lymphocytic infiltrate (tumor infiltrating lymphocytes – TILs).(Wilentz et al. 2000). The tumor has usually pushing border type periphery with no distinct invasive nature (1816). On molecular ground medullary carcinoma is often microsatellite instable and the patients may potentially benefit form immunotherapy (Le et al. 2015).

Invasive micropapillary carcinoma – in which >50% of the tumor is formed by the nests of cells suspended in small lacunae and the orientation of the epithelial cells is inversed, the neutrophilic infiltrate in epithelial cells is also the feature of this subtype (WHO 2019). This is an aggressive subtype of the PDAC with worse prognosis.

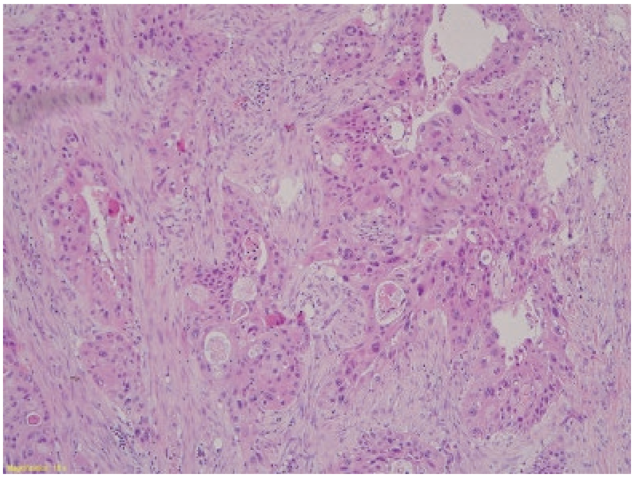

Figure 5 Adenosquamous carcinoma of the pancreas H&E x10.

Undifferentiated carcinoma – when the tumor cells proliferative without forming any recognizable glandular structures, the cells are discohesive and the stroma is sparse (Strobel et al. 2011). The tumor cells express at least focally cytokeratin which proves their epithelial nature and vimentin (which is not a feature of PDAC) (Paal et al. 2001) but the presence of intercellular adhesion marker E-cadherin is typically negative. This subtype is highly aggressive.

Undifferentiated carcinoma with osteoclast-like giant cells – the special subtype of PDAC where atypical and poorly differentiated epithelial component is accompanied by a mononuclear histocytic component and nonneoplastic osteoclast-like multinucleated giant cells (Muraki et al. 2016).

The other extremely rare histological subtypes of PDAC include: hepatoid carcinoma, signet-ring cell (poorly cohesive cell) carcinoma, choriocarcinoma, clear cell carcinoma, oncocytic carcinoma (WHO 2019).

Acinic Cells Carcinoma of the Pancreas

Histologically these tumors are formed by proliferation of monotonous neoplastic acinar cells accompanied by scant fibrous stroma and the foci of necrosis. Nuclei are uniform with single nucleolus and the cytoplasm is abundant, granular, and contain PASD positive granules. The architectural patterns include acinar, glandular, trabecular, and solid proliferations and the squamoid features are absent (La Rosa et al. 2012). In well-differentiated cases acinic cell carcinoma resembles normal nonneoplastic acini and the absence of pancreatic duct and the islets is then the helpful diagnostic element. Immunohistochemically acinic cell carcinoma expresses trypsin, chymotrypsin and BCL10 which performed together is sensitive enough for the diagnosis. Acinic cell carcinoma has to be differentiated form neuroendocrine tumors and pancreatoblastoma, particularly in the face of fact that acinic cell carcinoma is the most common type of pancreatic carcinoma in children (La Rosa et al. 2015).

Acinic cell carcinoma differs molecularly form PDAC and usually lack the most common mutations of *KRAS, SMAD4* and *CDKN2A* found in PDAC. The tumor shows chromosomal instability with high TMB and low levels of methylation. No genetic alteration may be considered typical of acinic cell carcinoma and the genetic mutations described in acinic cell carcinoma include: *MYC, APC*, and *CTNNB1* and *TP53* (Klimstra et al. 2016).

Genomics of Hepatic and Pancreatic Cancer

Hepatic cancer is probably best studied. The commonest cause world-wide is due to viral infection and a recent large series of whole genome structural variant analysis STVs has been conducted. The oncogenic changes are found in both coding and non-coding regions of the genome. In particular, a significant association with replication timing and identified known (CDKN2A, CCND1, APC, and TERT) and new (ASH1L, NCOR1, and MACROD2) cancer-related genes that were recurrently affected by STVs, leading to altered expression. These comprehensive and complex changes indicate the difficulty of identifying and therapeutically abrogating potential driver mutations (Fujimoto A 2016).

In pancreatic carcinoma over 30 recurrently mutated genes were identified. However, in signaling/functional in silico analyses these could be aggregated into 10 pathways: KRAS, TGF-β, WNT, NOTCH, ROBO/SLIT signaling, G1/S transition, SWI-SNF, chromatin modification, DNA repair and RNA processing. Furthermore, expression analysis defined four subtypes: (1) squamous; (2) pancreatic progenitor; (3) immunogenic; and (4) aberrantly differentiated endocrine exocrine (ADEX) that correlate with histopathological and molecular pathological characteristics (Bailey P 2016).

Key Take Home Messages

- The diagnosis of hepatocellular, cholangio-cellular and pancreatic carcinomas is based on histology and/or cytology.
- This diagnosis has to be made in the context of clinical data and with the results of immunohistochemical and molecular studies.
- It is to be underlined that there are no specific markers pathognomonic for cancers arising in these areas.
- The morphomolecular subtypes selection is vital for recruiting patients amenable to personalized anticancer treatment.
- The prognosis of hepatocellular cancer and ductal adenocarcinoma of the pancreas, aside from staging, can be fine-tuned by detailed pathology and molecular pathology sub-classification.

Areas for Further Research

- Methods of harvesting tissue material for cancer diagnosis specially in pCCAs and dCCAs
- Identification of more specific immunohistochemical markers for hepatic, biliary tracts and pancreatic cancers diagnosis and differentiation
- Further studies on molecular subtypes to fully cover the whole morphological spectrum of the lesions
- Individualization of treatment in patients with hepatic, biliary tracts, and pancreatic cancers based on detailed morphomolecular diagnosis
- The genomics of those most likely to develop hepatocellular cancer.

Trusted Websites for Further Reading

- College of American pathologists https://www.cap.org/member-resources/pathology-case-challenge/liver-4
- Pubmed https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2020752
- WHO https://www.who.int/health-topics/cancer#tab=tab_1

References

Abou-Alfa, G.K., Macarulla, T., Javle, M.M. et al. (2020). Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet* 21: 796–807.

Akita, M., Fujikura, K., Ajiki, T. et al. (2017). Dichotomy in intrahepatic cholangiocarcinomas based on histologic similarities to hilar cholangiocarcinomas. *Mod Pathol* 30: 986–997.

Bailey, P., Chang, D.K., Nones, K. et al. (2016). Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 531: 47–52.

Borazanci, E., Millis, S.Z., Korn, R. et al. (2015). Adenosquamous carcinoma of the pancreas: molecular characterization of 23 patients along with a literature review. *World J Gastrointes Oncol* 15: 132–140.

Braconi, C., Roessler, S., Kruk, B. et al. (2019). Molecular perturbations in cholangiocarcinoma: is it time for precision medicine? *Liver Int* 39: 32–42.

Burt, A.D., Alves, V., Bedossa, P. et al. (2018). Data set for the reporting of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinima and hepatocellular carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Histology* 68 (4): 369–385.

Calderaro, J., Couchy, G., Imbeaud, S. et al. (2017) Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumor classification. *J Hepatol* 67 (4): 727–738.

Collisson, E.A., Bailey, P., Chang, D.K., and Biankin A.V. (2019). Molecular subtypes of pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 16: 207–220.

Dursun, N., Feng, J., Basturk, O. et al. (2010). Vacuolated cell pattern of pancreatobiliary adenocarcinoma: a clinicopathological analysis of 24 cases of a poorly recognized distinctive morphologic variant important in the differential diagnosis. *Virchows Arch* 457: 643–649.

Fizazi, K., Greco, F.A., Pavlidis, N. et al. (2015). Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26: 133–138.

Fujimoto, A., Furuta, M., Totoki, Y. et al. (2016). Whole-genome mutational landscape and characterization of noncoding and structural mutations in liver cancer. *Nat Genet* 48: 500–509.

Graham, R.P., Barr Fritcher, E.G., Pestova, E. et al. (2014) Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. 45. 1630–1638.

Graham, R.P. and Torbenson, M.S. (2017). Fibrolamellar carcinoma: a histologically unique tumor with unique molecular findings. *Semin Diagn Pathol* 34 (2): 146–152.

Han, D.H., Choi, G.H., Kim, K.S. et al. (2013). Prognostic significance of the worst grade in hepatocellular carcinoma with heterogenous histologic grades of differentiation. *J Gastroenterol Hepatol* 28 (8): 1384–1390.

Klimstra, D.S. and Adsay, V.. (2016). Acinar neoplasms of the pancreas-A summary of 25 years of research. *Semin Diagn Pathol* 33: 307–318.

Kosmahl, M., Pauser, U., Anlauf, M., and Klöppel, G. (2005). Pancreatic ductal adenocarcinomas with cystic features: neither rare nor uniform. *Mod Pathol* 18: 1157–1164.

La Rosa, S., Adsay, V., Albarello, L. et al. (2012). Clinicopathologic study of 62 acinar cell carcinomas of the pancreas: insights into the morphology and immunophenotype and search for prognostic markers. *Am J Surg Pathol* 36: 1782–1795.

La Rosa, S., Sessa, F., and Capella, C. (2015). Acinar cell carcinoma of the pancreas: overview of clinicopathologic features and insights into the molecular pathology. *Front Med* 2 (14).

Labib, P.L., Goodchild, G., and Pereira, S.P.. (2019). Molecular pathogenesis of cholangiocarcinoma. *BMC Cancer* 19: 185.

Le, D.T., Uram, J.N., Wang, H. et al. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *N Eng J Med* 372: 2509–2520.

Li, T., Fan, J., Qin, L.X. et al. (2011). Risk factors, prognosis and management of early and late intrahepatic recurrence after resection of primary clear cell carcinoma of the liver. *Am Surg Oncol* 18 (7): 1955–1963.

Maruki, Y., Morizane, C., Arai, Y. et al. (2021). Molecular detection and clinicopathological characteristics of advanced/recurrent biliary tract carcinomas harboring the FGFR2 rearrangements: a prospective observational study (PRELUDE study). *J Gastroenterol* 56: 250–260.

Moeini, A., Sia, D., Zhang, Z. et al. (2017). Mixed hepatocellular cholangiocarcinoma tumors: cholangiolocellular carcinoma is a distinct molecular entity. *J Hepatol* 66: 952–961.

Muraki, T., Reid, M.D., Basturk, O. et al. (2016). Undifferentiated carcinoma with osteoclastic giant cells of the pancreas: clinicopathologic analysis of 38 cases highlights a more protracted clinical course than currently appreciated. *Am J Surg Pathol* 40: 1203–1216.

Nault, J.C., Calderaro, J., Di Tommaso, L. et al. (2014). Telomerase reverse transcriptase promotor mutation is an early somatic genetic alteration in the transformation of premalignant nodules in hepatocellular carcinoma on cirrhosis. *Hepatology* 60 (6): 1983–1992.

Paal, E., Thompson, L.D., Frommelt, R.A. et al. (2001). A clinicopathologic and immunohistochemical study of 35 anaplastic carcinomas of the pancreas with a review of the literature. *Ann Diagn Pathol* 5: 129–140.

Rhee, H., Kim, H., and Park, Y.N.. (2020). Clinico-radio-pathological and molecular features of hepatocellular carcinomas with keratin 19 expression. *Liver Cancer* 9: 663–681.

Rizvi, S., Khan, S.A., and Hallemeier, C.L. (2017). Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 15: 95–111.

Saha, S.K., Parachoniak, C.A., Ghanta, K.S. et al. (2014). Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. *Nature* 513: 110–114.

Schulze, K., Imbeaud, S., Letouzé, E. et al. (2015). Exome sequencing of hepatocellular carcinoma identifies new mutational signatures and potential therapeutic target. *Nat Genet* 47 (5): 505–511.

Seok, J.Y., Na, D.C., Woo, H.G. et al. (2012). A fibrous stromal component in hepatocellular carcinoma reveals a cholangiocarcinoma-like gene expression trait and epithelial-mesenchymal transition. *Hepatology* 55 (6): 1776–1786.

Shlitter, A.M., Segler, A., Steiger, K. et al. (2017). Molecular, morphological and survival analysis of 177 resected pancreatic ductal adenocarcinomas (PDACs): Identification of prognostic subtypes. *Sci Rep*.

Sciarra, A., Park, Y.N., and Sempoux, C. (2020). Updates in the diagnosis of combined hepatocellular-cholangiocarcinoma. *Hum Pathol* 96: 48–55.

Strobel, O., Hartwig, W., Bergmann, F. et al. (2011). Anaplastic pancreatic cancer: presentation, surgical management, and outcome. *Surgery* 149: 200–208.

Torbenson, M.S. (2017). Morphologic subtypes of hepatocellular carcinoma. *Gastroenterol Clin North AM* 46: 365–391.

Wada, Y., Nakashima, O., Kutami, R. et al. (1998). Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. *Hepatology* 27: 407–414.

(2019). WHO Classification of Tumors Editorial Board. Digestive system tumors. International Agency for Research on Cancer.

(2010). WHO Classification of Tumors Editorial Board. Digestive system tumors. International Agency for Research on Cancer.

Wilentz, R.E., Goggins, M., Redston, M. et al. (2000). Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: a newly described and characterized entity. *Am J Pathol* 156: 1641–1651.

16 Screening, Surveillance, and Prevention of Hepatocellular Carcinoma

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Introduction

Hepatobiliary cancer refers to any malignancy affecting the liver, bile ducts, or gall bladder. HCC is the most common form of primary liver cancer and poses a significant global health issue. According to the World Health Organisation (WHO), at present it is the fifth-most commonly diagnosed cancer and fourth-leading cause of cancer-related mortality worldwide (Bray et al. 2018). These cancers are associated with a high mortality, as patients are often asymptomatic until late in the disease pathogenesis whereby curative treatments are no longer an option. In this chapter we will be focusing specifically on the screening, surveillance, and prevention of Hepatocellular Carcinoma (HCC).

Risk Factors

The majority of HCC cases will occur in individuals with established risk factors for chronic liver disease, these factors include but are not exclusive to non-alcoholic fatty liver disease (NAFLD), heavy alcohol consumption, chronic viral hepatitis (specifically hepatitis B and C viruses), haemachromatosis and rarer causes such as inborn errors of metabolism or specific autoimmune diseases(Akinyemiju et al. 2017; El-Serag and Rudolph 2007) (see Table 1 for summary). The risk factors for development of HCC are also risk factors for liver cirrhosis, which is estimated to be present in 90% of patients diagnosed with HCC in the Western World (Llovet et al. 2021). For this reason, it is not cost-effective or indeed necessary for a national screening program to take place in the general population. However, current expert society guidance recommends regular surveillance for patients with established risk factors for HCC (Foerster and Galle 2019) and those with underlying liver cirrhosis.

Liver Cirrhosis and Relationship to HCC

Cirrhosis is defined as chronic liver disease characterized by diffuse fibrous changes and progressive disruption to normal liver architecture which results in portal hypertension, synthetic dysfunction, and ultimately liver failure (Ginés et al. 1987). It is a complex cascade of molecular, cellular, and structural changes which accumulate over time and predispose to the malignant transformation of hepatocytes. Liver cirrhosis is associated with a chronic inflammatory state, this is a result of the release of endogenous damage-associated molecular patterns (DAMPs) when the extracellular matrix of hepatocytes is broken down following repeated exposure to insults (Kono and Rock 2008). Cirrhosis is also strongly associated with multi-organ failure and can lead to coexisting kidney failure, coagulopathy, brain dysfunction, as well as circulatory collapse, immunosuppression, and disruption of the intestinal microbiome (Arroyo et al. 2016). There are a number of classification systems used to grade the severity of liver cirrhosis, for example the Child-Pugh Classification System and the Model for End-Stage Liver Disease (MELD) score. Universally, Child-Pugh Classification is the most commonly used to define the severity of liver dysfunction and associated prognosis, it uses a number of variables including values of bilirubin, prothrombin time, and albumin, in addition to the presence of encephalopathy and ascites (Angermayr et al. 2003; Cooper et al. 1997). Child-Pugh C carries the worst prognosis with a less than <50% one year survival rate, this is statistically worse than many cancers (D'Amico et al. 2006).

While the majority of patients who develop HCC will have underlying liver cirrhosis, it is worth noting that HCC can develop in the absence of underlying cirrhosis in various circumstances. For example, the Hepatitis B Virus is a double stranded DNA virus that directly alters hepatocyte DNA (Iannacone and Guidotti 2022) by integrating into the host genome. The process of integration can lead to genetic mutations which can result in either oncogene activation and/or deactivation of tumor suppressor genes (Yuen et al. 2018). Disruption to these genes can lead to malignant transformation

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Table 1 A summary of the major risk factors for the development of Hepatocellular Carcinoma.

Infectious	Chronic Hepatitis B (HBV) infection
	Chronic Hepatitis C (HCV) infection
	HIV
	Liver Flukes
Toxins	Alcohol
	Aflatoxins
	Drug-induced liver injury (DILI)
Autoimmune	Autoimmune hepatitis (AI)
	Primary biliary sclerosis
	Primary sclerosing cholangitis
Metabolic syndrome	Non-alcoholic fatty liver disease (NAFLD)
	Diabetes, hyperlipidemia, obesity
Inborn errors of metabolism	Hereditary haemochromatosis
	Wilson's disease
	Alpha-1-antitrypsin deficiency
Congenital	Biliary atresia
	Congenital hepatic fibrosis

Table adapted from Chidambaranathan-Reghupaty et al. (2021).

of cells in the absence of cirrhosis and it is for this reason that HCC surveillance is recommended for patients with chronic Hepatitis B Virus, even those with normal liver architecture (Anugwom et al. 2021).

Pathogenesis of Hepatocellular Carcinoma (HCC)

HCC is, by nature, a highly heterogeneous malignancy with molecular patterns that vary patient to patient. It is this variation that makes HCC difficult to target with systemic therapies; there is a distinct lack of a common molecular target. Notwithstanding, the use of next-generation genomic sequencing has identified a number of key mutations which are central to HCC tumorigenesis. Approximately ~140 genes have been identified to promote malignant transformation of cells in any cancer, with a typical tumor containing between 2–8 of these "driver" mutations which confer a selective growth advantage, while the remaining mutations are neutral passengers that are neither favorable or unfavorable to carcinogenesis (Vogelstein et al. 2013). Genetic risk factors and events involved in HCC carcinogenesis can broadly arise in three ways: inherited genetic variants, acquired somatic mutations, and integration of viral DNA into the host genome (Caruso et al. 2021) (Figure 1).

Susceptibility to HCC is multifactorial, involving both genetic and environmental factors. There are a number inherited single-nucleotide polymorphisms (SNPs) which affect the predisposition to risk factors associated and severity of liver disease. SNPs refer to DNA sequence modification caused by variation in a single nucleotide; many SNPs occur within a non-coding stretch of DNA material, they can modify gene-product expression and associated function if they occur within coding DNA (Nahon and Zucman-Rossi 2012). SNPs generally account for ~90% of allelic variation within the human population (Andreassen et al. 2002); this contributes to how individuals are differently affected by disease.

A number of genetic polymorphisms have been shown to increase the incidence and severity of NAFLD. The *PNPLA3* gene is expressed in liver and adipose tissue, it is thought to play a role in lipolysis and triglyceride hydrolysis (Hassan et al. 2013). Certain alleles of *PNPLA3* have been shown promote triglyceride accumulation within hepatocytes and subsequently increase the risk of NAFLD, particularly in patients with high chronic alcohol intake (Romeo et al. 2008). Interestingly, the toxicity of the carcinogen Aflatoxin B1 has been shown to be potentiated by HBV infection, particularly in individuals who carry a null polymorphism in *GSTT1* (Wang et al. 2010). Functionally, GST encodes Glutathione-S-transferases which are involved in the detoxification of substances through the process of conjugation. A small number of individuals are able to constitutionally clear themselves of HCV infection without any treatment. A number of pivotal GWAS studies linked a particular SNP located in the Interleukin-28B (IL-28B) gene to a much higher probability of natural clearance of HCV by the host (Rauch et al. 2010; Thomas et al. 2009). The ability to clear HCV reduces the chance of chronic inflammation and cirrhosis, which in turn reduces the likelihood of going on to develop HCC.

Somatic mutations are acquired during a lifetime; certain mutations can result in aberrant disruption of downstream molecular pathways and play a key role in HCC carcinogenesis. Telomerase is activated in over 80% of HCCs, this occurs through various different mechanisms including TERT promoter mutations, viral DNA insertions or chromosome translocation (Guichard et al. 2012). The most frequent site of HBV DNA insertion and mutagenesis involves the TERT promoter region, the subsequent over expression of telomerase results in maintenance of telomere length. These lengthened telomeres protect hepatocytes from cellular senescence and promote ongoing replication (Nault et al. 2019). Other dysregulated pathways include the beta-catenin/Wnt pathway which promotes HCC stem cell features and prevents apoptosis of malignant cells, this occurs in approximately 50% of HCCs (Guichard et al. 2012).

Receptor-Tyrosine Kinase (RTK) pathways have also been implicated in the development of HCC as with many other

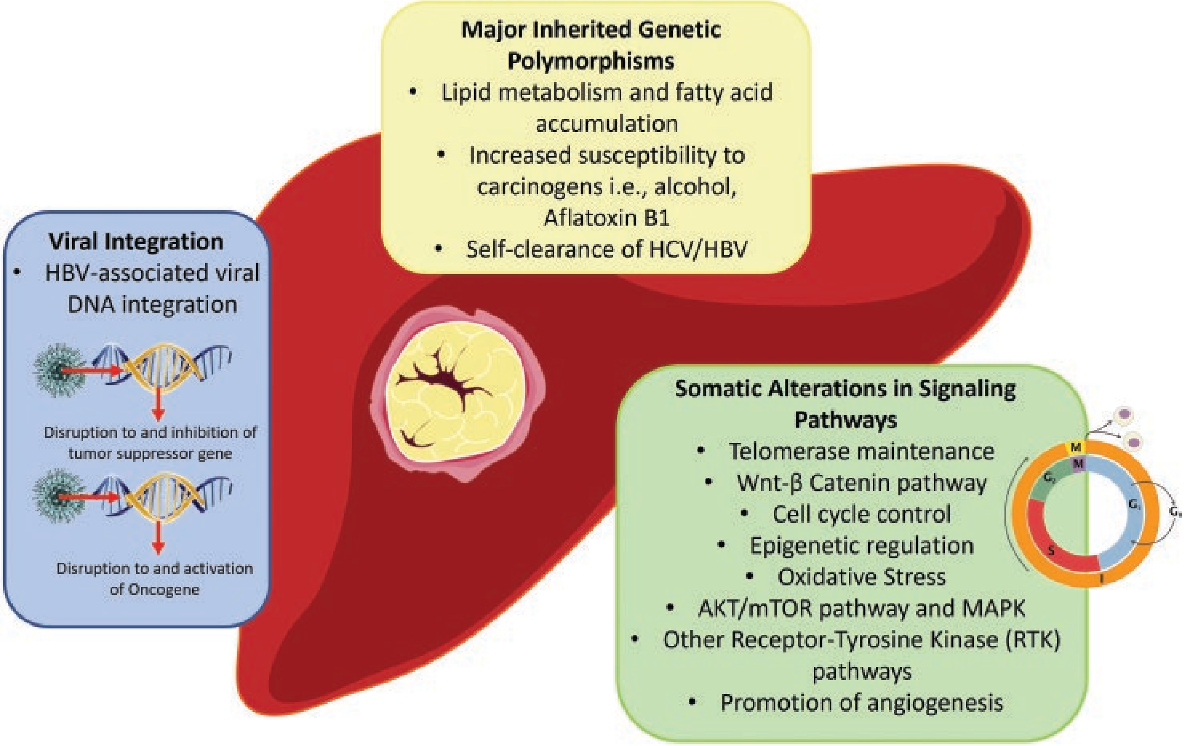
Major Inherited Genetic Polymorphisms
• Lipid metabolism and fatty acid accumulation
• Increased susceptibility to carcinogens i.e., alcohol, Aflatoxin B1
• Self-clearance of HCV/HBV
Viral Integration
• HBV-associated viral DNA integration
Disruption to and inhibition of tumor suppressor gene
Disruption to and activation of Oncogene
Somatic Alterations in Signaling Pathways
• Telomerase maintenance
• Wnt-β Catenin pathway
• Cell cycle control
• Epigenetic regulation
• Oxidative Stress
• AKT/mTOR pathway and MAPK
• Other Receptor-Tyrosine Kinase (RTK) pathways
• Promotion of angiogenesis
M
M
G1
G0
S

Figure 1 Diagram demonstrating three distinct genetic mechanisms involved in HCC Carcinogenesis. Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; mTOR, mammalian target of rapamycin; RTK, receptor-tyrosine kinase.

cancers. RTKs are a subfamily of different receptors including vascular endothelial growth factor (VEGF), hepatocyte growth factor receptor (HGFR), tie 2 and RET (Regad 2015; Robinson et al. 2000); binding of a ligand to its specific RTK causes phosphorylation of target proteins involved in downstream signaling pathways (Gotink and Verheul 2010). Mutations affecting RTK function, genetic amplification, translocation, or the autocrine activation of RTKs can lead to downstream aberration of oncogenic pathways which lead to tumorigenesis, local invasion, and angiogenesis (Sudhesh Dev et al. 2021). HCC is a highly angiogenic cancer and relies heavily on the formation of new blood vessels in order to sustain growth (Andrew X Zhu et al. 2011). The net excess secretion of pro-angiogenic cytokines in HCC, such as VGEF, results in the proliferation and migration of endothelial cells which form cord precursors to blood vessels (Dvorak 2002). Arterialization of HCC, compared to the vascularization of surrounding non-malignant liver parenchyma, can be exploited for diagnosis and treatment; this will be discussed in more detail later in the chapter.

Environmental risk factors for HCC are largely avoidable, if the population were able to maintain a healthy lifestyle by avoiding alcohol, keeping a healthy BMI, and not partaking in practices that carry a risk of contracting the Hepatitis B or C virus, they could effectively reduce their risk of developing this type of cancer. However, this ignores the complexity of the factors at play which contribute to humans making choices that can have negative impact on their health. Lifestyle risk factors are not unique to HCC, the risk of most cancers increases with exposure to carcinogens such as smoking in lung cancer and the Human Papillomavirus (HPV) in cervical cancer (Psyrri and DiMaio 2008). In a utopian reality we would be able to empower patients to only make choices that benefit their health and eliminate exposure to risk factors. This, of course, is an impossible task and while prevention is better than cure, surveillance is a necessary strategy that aims to reduce the morbidity and mortality associated with HCC.

Surveillance

Surveillance is the systematic and ongoing process used to monitor a disease condition in patients deemed to be at higher risk (Pelletier et al. 2005). This differs from screening which is the active search for disease amongst a seemingly healthy population (Oleske 2009). In relation to HCC, surveillance is the more appropriate terminology to use as the process takes place in patients who high risk for HCC development due to the presence of established risk factors.

The ideal surveillance program for any type of cancer should be minimally invasive, highly sensitive, specific, inexpensive, and easy to implement in a clinical setting (Fitzmorris and Singal 2015) with the aim of identifying cancer early to give the best possible chance of cure. In relation to HCC, early detection makes it more likely that the cancer will be amenable to potentially curative treatments such as radiofrequency or microwave ablation, surgical resection, or liver transplantation (Kanwal and Amit G Singal 2019). Surveillance methods and strategies for HCC have long been a subject of debate, in this section of the chapter we will give an overview and discuss the evidence base for current practice and future directions.

International guidance has been published to give clinicians around the world access to the best evidence-based practice so that they can provide the best possible care for their patients. There are three main international bodies who have produced robust guidance on HCC surveillance, these are the European Association for the Study of the Liver (EASL), American Associated for the Study of Liver Diseases (AASLD) and the Asian Pacific Association for Study of the Liver (APASL) (Foerster and Galle 2019). We have discussed how HCC has a much higher incidence in individuals with liver cirrhosis compared to that of the general population, it therefore is logical that HCC surveillance is focused on this patient cohort. The annual incidence of HCC in patients with cirrhosis ranges from 1–6% (Trinchet et al. 2015) although this does vary with different underlying etiologies. For patients with viral or autoimmune related cirrhosis the adjusted relative risk of developing HCC is 2–3 fold compared to alcoholic liver cirrhosis (West et al. 2017), although the exact reason for this disparity is not fully understood. The AASLD has produced guidance on this subject, it states that surveillance should be offered to patients when their relative risk of HCC exceeds 1.5% per annum based on cost-effectiveness data (Bruix et al. 2011), interestingly by these standards surveillance in alcohol related cirrhosis is only just considered cost-effective.

It is important to consider that certain risk factors for HCC are more or less prevalent in different populations and this will inevitably have an impact on surveillance programs. Even within the West there is a big variation in the predominance in these etiological risk factors, for example in North America the HCV epidemic has been the most common cause of hepatocarcinogenesis whereas in Central and Eastern Europe, alcohol consumption is the major player (Singal et al. 2020). Contrastingly, in many countries in South East Asia (with the exception of Japan) HBV associated HCC is far more common in the population compared to other lifestyle related risk factors (Terrault et al. 2018). This is in part due to barriers accessing testing and vaccination as well as a lack of education as to the mode of viral transmission which is predominantly through sexual contact, injecting drug use, and also vertical transmission (Wait et al. 2016). Both the East and West follow the same general consensus on methods of HCC surveillance set out by the international societies; however, they do adopt different approaches with regards to how these methods are implemented. For example, in the West the uptake of surveillance is lower and relies on individual compliance and choice rather than a nationwide approach. A systematic review of US studies found that only 20% of eligible individuals underwent HCC surveillance (Singal et al. 2012). Contrastingly, in South East Asian countries such as Japan, national surveillance programs exist in part due to endemic nature of HBV/HCV within the population. As a result, the majority of HCC cases are detected at an early stage and with an average 45% five-year survival rate (Kudo 2012), which is clearly superior to the average international statistic of 20% five-year survival rate for HCC (Siegel et al. 2018).

An Introduction to Radiology in the Surveillance of Hepatocellular Carcinoma

Radiology currently forms the basis of HCC surveillance. Current GOLD standard methods recommended in all guidelines include the use of Ultrasonography (US), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in the surveillance and diagnosis of HCC (Foerster and Galle 2019).

Ultrasound (US)

Ultrasound (US), or Ultrasonography, is an imaging modality that uses high-frequency sounds waves to produce real time images of structures within the body. It is a very safe, non-invasive and an inexpensive technique which makes it favorable in the screening and diagnosis of HCC (Harris et al. 2019). These factors are the reason that US currently forms the backbone of HCC surveillance; current guidance recommends that patient with cirrhosis undergo six-monthly check-ups for HCC with ultrasonography screening (Barbara et al. 1992). Globally, the consensus of the six-monthly time frame interval is based on evidence that survival rates are better compared to annual screening but without inferior outcomes compared to three-monthly testing (Trinchet et al. 2011). There has been a single randomized controlled trial (RCT) which has evaluated the outcomes of surveillance vs. no surveillance in 18,816 patients with Hepatitis B infection in China. The trial looked specifically at the use of liver US and serum alpha-fetoprotein (AFP) measurements as the means of surveillance and showed a 37%

reduction in HCC related mortality at five-year follow up in the surveillance group (Zhang et al. 2004).

The classical US appearance of a small focal HCC is a hypoechoic nodule when compared to surrounding liver architecture. Larger lesions are more likely to be heterogeneous in appearance as a consequence of inflammation, fatty infiltration, necrosis, and calcification (Venkatesh et al. 2014). Ultrasound is not used to definitively diagnose HCC but rather to identify suspicious lesions which will go on to be evaluated further with contrast CT, MRI, or USS. The majority of lesions < 1cm are difficult to diagnose and often do not represent HCC so in this instance cross-sectional imaging is not recommended, rather follow up with repeat ultrasonography in three months (Marrero et al. 2018). By contrast, guidance suggests that lesions measuring >1cm in diameter should be further evaluated with CT or MRI the role of which will be discussed later in this chapter.

An important factor to consider when evaluating the use of ultrasound is that the sensitivity is often operator dependent. The ability to accurately scan and detect a possible HCC lesion will depend heavily on the experience and skill set of the individual performing the scan, this can vary dramatically. For example, a large scale meta-analysis looked at studies evaluating the sensitivity of US in detection of any-stage HCC found a huge variation in sensitivity from 28% to 100% (Tzartzeva et al. 2018). Not only does the sensitivity vary between operators, the sensitivity for HCC detection also depends on the stage of the cancer at point of detection. The same meta-analysis showed that the pooled sensitivity was 84% however significantly lower for early-stage HCC detection at only 47%. This poses an issue in that detection of early HCC, the very aim of surveillance, is much less sensitive compared to more advanced HCC which are less likely to be cured. Interestingly, the sensitivity of US is also lower in patients with advanced cirrhosis. This phenomena is thought to be due to the increased nodularity and coarse texture of the liver which distorts the ultrasound images (Andreana et al. 2009); this is clearly a significant pitfall given that the majority of patients under surveillance will have cirrhosis. In practice, patient factors will also have an impact on the ability of US to detect HCC. For example, patients with NAFLD as the causative etiology for their cirrhosis are more likely to be overweight or obese. Large body habitus limits the quality of US images and increases the likelihood of a false negative result (Esfeh et al. 2020), this means that patients may go on to have more invasive scans which carry a risk of ionizing radiation such as CT.

To improve its sensitivity, US can be used in conjunction with serum alpha-fetoprotein (AFP) measurements when monitoring for HCC development. AFP is the only validated and widely accepted biomarker for surveillance (Tayob et al. 2019) but remains controversial; this will be discussed in more detail later in this chapter.

Computed Tomography (CT)

The GOLD Standard imaging technique for the diagnosis of HCC is a CT liver triple-phase with delayed contrast sequences, this exploits the unique vascular properties of HCC which make it distinct from other types of malignancy. CT as standard practice is endorsed by all of the international societies for the study of liver disease and whilst US is the mainstay of surveillance, CT is superior in the diagnosis of HCC as images confer a higher sensitivity and specificity.

Hepatocarcinogenesis occurs stepwise fashion of progressive cellular de-differentiation of cirrhotic nodules to dysplastic nodules. Over time dysplastic cells replace the surrounding cirrhotic tissue, as these cells are cloned and replicated they will eventually produce nodules with a malignant phenotype (Choi et al. 2014). The described process does not occur in isolation; often carcinogenesis is occurring simultaneously in multiple areas of the liver parenchyma as cirrhosis affects the whole organ; this explains why once a patient has been diagnosed with one HCC, their risk of further lesions rises exponentially (Kim et al. 2020). In normal anatomy, the liver is unique in that it receives dual blood supply from the hepatic artery and the hepatic portal vein. These vessels are also paired with a bile duct to form a structure referred to as the portal triad. As a HCC develops it recruits arteriolar blood supply through secretion of angiogenic growth factors, such as vascular endothelial growth factor (VGEF) (Andrew X. Zhu et al. 2011). As a consequence, a HCC will receive the majority of its blood supply via arterial collaterals and gradually loses its venous supply (illustrated in Figure 2) (Morse et al. 2019); it is this phenomena that is exploited for the diagnosis of HCC using contrast-enhanced triple phase CT.

Contrast is injected and images are taken during the arterial phase, this results in high uptake of contrast in the HCC lesion due to its high arterial vascularity; a process called enhancement. Following this, images are then taken during the portal venous phase and the delayed acquisition phase at 3–5 minutes post contrast injection (Shah et al. 2014). During these phases, there is a characteristic “washout” pattern, regarded as the radiological hallmark of HCC. This washout pattern has an overall sensitivity of 89% and specificity of 96% for pooled any stage HCC (van der Pol et al. 2019) making it an excellent imaging modality for diagnosis without the need for histological confirmation with biopsy which is a stark difference to most other cancers which require biopsy for GOLD standard diagnosis. The ability to diagnose cancer without biopsy is a clear advantage, particularly in patients with liver disease who often have a coagulopathy as a result of synthetic liver dysfunction and for which bleeding would be a significant risk with any invasive procedure. Bleeding following liver biopsy occurs in approximately 3–4% of cases, with

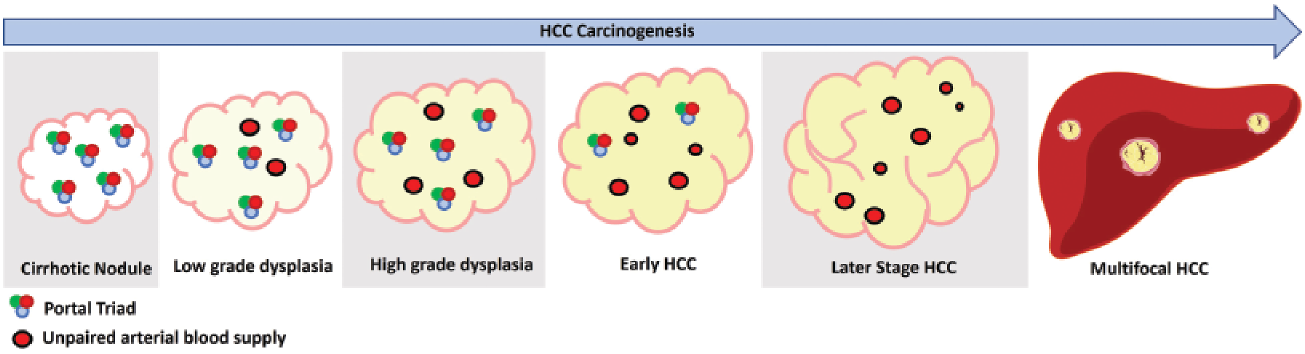

Figure 2 Image demonstrating carcinogenesis in HCC and progressive adaptation of vasculature from normal anatomy with portal triad supply to progressive angiogenesis and unpaired arterial supply. Abbreviations: HCC, hepatocellular carcinoma. Adapted from Yang and Poon (2008).

0.5% of these categorized as severe requiring blood transfusion (Rockey et al. 2009). Furthermore, there is a risk of tumor seeding following needle biopsy which can lead to hematological spread of malignant cells and distant metastasis. The incidence of tumor seeding was originally reported at 0.9% per year (Silva et al. 2008) although subsequent studies have shown a lower risk of 0.14–0.76% (Chang et al. 2008; Szpakowski et al. 2017). Tumor seeding potential is less of a problem with advanced disease, however in isolated primary tumors it may increase the risk of disease progression (Childs et al. 2021). The ability to diagnose HCC without biopsy is advantageous to patients on an individual basis; however there is debate as to whether lack of access to histology has actually delayed our understanding of the molecular pathogenesis of HCC compared to other cancers. In the last few decades we have seen the emergence of cancer-specific, targeted therapies come to market, for example monoclonal antibodies (mAb) such as Trastuzumab (Herceptin) in the treatment of breast HER2 positive breast cancer (Wilson et al. 2017) and the use of anti-androgen hormone therapies in prostate cancer (Rice et al. 2019). It is the wide availability of tissue histology from these cancers that has made it possible for these targeted treatments to be developed, arguably this is something comparatively lacking in HCC research.

As with any imaging modality, the sensitivity of CT is also dependent on the tumor size. Smaller lesions are invariably more difficult to detect, a confident diagnosis of HCC has been shown to not be feasible for sub centimeter (<1 cm) nodules (Bruix et al. 2011; Forner et al. 2008) which accounts for why lesions < 1cm are re-evaluated in three months from initial identification rather than being subject to further investigation. It is pertinent to consider that not all HCCs will have the characteristic radiological features described previously. Approximately 30% of HCCs will have an atypical appearance (Bruix et al. 2011) and will require biopsy for further evaluation, atypical appearance is more likely to be a feature in smaller, well-differentiated HCCs (Kovac et al. 2021).

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is an excellent imaging modality that produces highly detailed images of soft tissues using a magnetic field and radio waves (Grover et al. 2015). A clear advantage of MRI is that it does not use ionizing radiation to produce images, therefore it is relatively risk free for patients. The lack of ionizing radiation is particularly advantageous in the context of a chronic disease whereby repeated scans may be required. MRI exploits the same vascular properties of HCC as CT, it relies on the contrast-enhanced and subsequent washout phase to diagnose HCC lesions. Several studies have showed superiority of MRI over CT in terms of sensitivity in detecting HCC (Noguchi et al. 2003; Semelka et al. 2001). A metanalysis of 11 studies showed superiority of contrast enhanced MRI sensitivity over CT for HCC lesions > 2cm (89% and 79% respectively) and < 1cm (69% and 49% respectively) however, there was no significant difference in specificity, positive likelihood ratio or the diagnostic odds ratio (Roberts et al. 2018).

While MRI has fantastic diagnostic capability, it is one of the most expensive imaging techniques used in modern clinical practice. Cost-effectiveness is often expressed using Quality Adjusted Life Years (QALYs) which measures the benefit of a health intervention given to a patient over the course of their lifetime at a certain cost. Different countries have different ideas as to what constitutes as a cost-effective threshold, in the UK the National Institute for Health and Care Excellence (NICE) uses a threshold between £20, 000–£30, 000 per QALY gained (McCabe et al. 2008); any intervention costing less than these figures is deemed a cost-effective strategy. The cost of one QALY gained by MRI HCC Surveillance has been reported to be as high as $100, 000 (Andersson et al. 2008). A systematic review evaluating the cost of different methods of HCC surveillance using US data found the average cost of MRI per scan to be $1400 (range $900–$1700) which compares to $640 for CT and $185 for US alone (Andersson et al. 2008). It is clear that it would not be a cost-effective strategy or indeed economically feasible to use MRI as the primary tool for surveillance of HCC. There are also other factors to consider with MRI for example, patients may have certain devices such as pacemakers, cochlear implants and neurostimulators that is, deep brain stimulator electrodes which are not MRI compatible.

LI-RADS Classification

The Liver Imaging Reporting and Data System (LI-RADS) has been developed to both standardize the interpretation and reporting of liver lesions (Santillan et al. 2018) detected on the different imaging modalities used in HCC surveillance. It is supported by the American College of Radiology (ACR) and was created by a multinational, multidisciplinary conglomerate of expert radiologists and specialists in liver cancer imaging (Chernyak et al. 2018). Radiological features of benign lesions such as simple cysts or haemangiomas will be classified as LI-RAD one-half representing benign or probably benign. Radiological features highly suggestive of malignancy for example target diffusion restriction, peripheral arterial enhancement or rim washout will be labeled in a higher risk LI-RAD category (LI-RADS grading system summarized in Table 2) (Marrero et al. 2018). Growth is also used as part of the major criterion in LI-RADS, any growth > 50% in six months is highly suspicious for HCC however, the lesion in question must be present on previous imaging (Chernyak et al. 2018).

Naturally, the creation and utilization of LI-RADS preceded the validation of evidence to support its use in clinical practice. There is now emerging evidence that strongly favors its use, a systematic review supports the “Major” criteria in LI-RADS HCC reporting namely arterial-phase enhancement (APHE), “washout” appearance and capsule appearance (Tang et al. 2018). It is consistently evaluated and updated in line with the best available evidence. The integration of LI-RADS into the AASLD guidance is based on the evidence that it significantly improves the standardization of reporting and accuracy of risk stratifying liver lesions (van der Pol et al. 2019). Although it is a predominantly American system, LI-RADS has a worldwide influence and guidance is used by clinicians globally to aid understanding and reporting of HCC. EASL currently has slightly different recommendations for the reporting of liver lesions (Berzigotti et al. 2021), in the future it would be ideal to see harmonization between different institutional guidance in order to achieve consensus on best practice management of liver disease among international experts. Figure 3 summarises the HCC surveillance pathway based on the LI-RADS criteria.

Table 2 Summary of LI-RADS classification for radiological description of liver lesions.

Definitions in the LI-RADS classification system	
LR-1	Benign
LR-2	Probably benign
LR-3	Intermediate probability of malignancy
LR-4	Probably HCC
LR-5	Definitely HCC
LR-M	Probably or definitely malignancy but not HCC
LR-TIV	Definitely tumor in vein
LR-NC	Unable to categorize due to image degradation

Abbreviations: LR, liver reporting; LI-RADS, Liver Imaging Reporting and Data System.

Surveillance Harms

Although there are clear benefits to surveillance in patients at high risk of HCC, it is important to consider the potential harms of these strategies. In terms of harms to the patient, these can be divided into physical and psychological harms (Heleno et al. 2013). With any test there is always a risk of a false-positive result if radiology is inconclusive or indeed suggestive of HCC the patient may go on to have an invasive investigation or interventional procedure. Prospective cohort studies have suggested that approximately 5% of individuals enrolled in HCC surveillance per year will go on to have unnecessary investigation and/or intervention (Trinchet et al. 2015). For example, radiofrequency ablation used in the management of small focal HCCs carries a risk of bleeding, infection, and damage to internal structures (Maeda et al. 2020). In relation to the harms of imaging specifically, repeated CT scans confer accumulative radiation exposure which can increase the risk of cellular damage and associated cancer, a risk that many patients are not counselled on. Furthermore, there is also an acute risk of contrast induced nephropathy which can lead to renal failure; this is of particular relevance in patients with cirrhosis (Safi et al. 2015) who may have associated hepatorenal syndrome in which their baseline kidney function is already poor and at risk of further deterioration.

For patients who have advanced cirrhosis with poor physiological reserve, surveillance is unlikely to infer any benefit. The rationale is that this cohort of patients will not be fit enough to survive invasive procedures or surgery thus, surveillance will not change the outcome for the patient (Taylor et al. 2017). It is important that patients are counseled on the purpose of surveillance and are aware of its limitations and the possibility that it can lead to a number of unnecessary investigations and even treatments. The British Society of

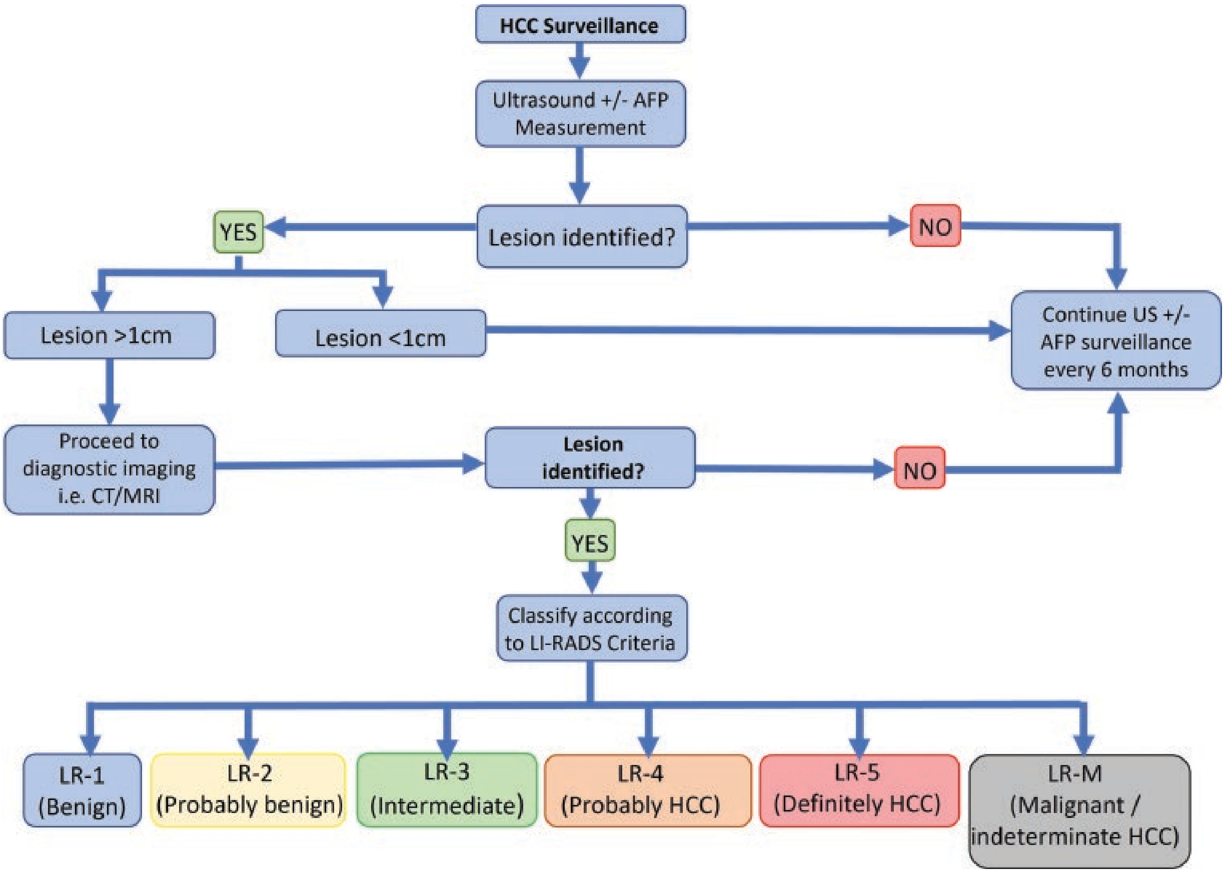
HCC Surveillance
Ultrasound +/- AFP Measurement
Lesion identified?
YES
NO
Lesion >1cm
Lesion <1cm
Continue US +/- AFP surveillance every 6 months
Proceed to diagnostic imaging i.e. CT/MRI
Lesion identified?
NO
YES
Classify according to LI-RADS Criteria
LR-1 (Benign)
LR-2 (Probably benign)
LR-3 (Intermediate)
LR-4 (Probably HCC)
LR-5 (Definitely HCC)
LR-M (Malignant / indeterminate HCC)

Figure 3 Summary of Hepatocellular Carcinoma (HCC) surveillance pathway in high-risk patients. Abbreviations: AFP, alpha-fetoprotein; CT, computed tomography, HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; LR, liver reporting; US, ultrasound; MRI, magnetic resonance imaging. Image adapted from Fitzmorris and Singal (2015); Moura Cunha et al. (2021).

Gastroenterology (BSG) published up to date best practice guidance for HCC surveillance in 2021 and recommends that patients who have liver cirrhosis classified with Child-Pugh C or Child-Pugh B7 Cirrhosis with uncontrolled ascites are not suitable for surveillance as they will not tolerate anticancer treatments, they can however be considered for liver transplantation(Kanwal and Amit G. Singal 2019).

Future Directions of Imaging in HCC Surveillance

In recent years, contrast enhanced ultrasound (CEUS) is a significant advancement from conventional US. CEUS produces real time images of focal liver lesions with the ability to assess the enhancement/washout pattern observed with contrast (Lyshchik et al. 2018) as used in other imaging modalities previously described. A key difference is the methodology of contrast administration, CEUS uses microbubble based contrast agents which are injected intravenously (Bartolotta et al. 2019). They consist of flexible phospholipid shells which contain soluble gas bubbles which remain within the intravascular space acting as purely vascular marker (Motz et al. 2021). A metanalysis evaluated use of CEUS for diagnosis of HCC, the pooled sensitivity of which was 92%, specificity 87%, diagnostic odds ratio (OR) 104 and a positive likelihood ratio of 0.09 (Wu et al. 2018).

Despite its advantages, CEUS has not been recommended in surveillance of HCC by EASL & AASLD. In part, this is due to its limited ability to distinguish between HCC and intrahepatic cholangiocarcinoma (ICC) (Vilana et al. 2010), which is another cirrhosis-associated malignancy that occurs in 1–5% of individuals with cirrhosis per year (Blechacz 2017). It also subject to the same limitations as conventional US such as operator dependence and patient factors (Kim et al. 2017). Additionally, it is only able to visualize one area of the liver at a time during contrast administration, this compares to CT/MRI which is able to analyze contrast uptake in the whole liver at any one time. In 2017, LI-RADS criteria was developed for use specifically in CEUS (Chernyak et al. 2018), similar in concept to the LI-RADS criteria used in CT/MRI, and has which has improved the standardization of reporting (Lee et al. 2021).

There have been no randomized controlled trials (RCTs) looking at HCC surveillance and non-surveillance in patient with cirrhosis(Julie K. Heimbach et al. 2018), largely because surveillance is widely accepted to be beneficial and it would be unethical to deprive patients from access to this for randomization purposes. Unfortunately, the hierarchy of evidence for surveillance is therefore limited and relies heavily on systematic reviews and metanalysis of observational cohort studies. Of the evidence available, one of the largest systematic reviews of 47 studies (which included a total of 15,158 patients) conducted in China demonstrated that surveillance more than doubled the chance of early tumor detection and of being offered curative treatment options (Singal et al. 2014). Surveillance was also significantly associated with improved pooled three-year survival rate of 50.8% compared to 27.9% for patients who presented symptomatically or diagnosed incidentally. Observational studies are subject to lead time bias and often studies to not take this into consideration when reporting statistical significance; this is something that must be considered when evaluating the evidence base.

Despite the widely accepted benefits, the uptake of HCC surveillance is notoriously poor with less than one in five patients estimated to be receiving surveillance globally (Singal et al. 2017). Of the 18,186 patients with HBV in the large RCT by Zhang et al., only 60% of subjects persistently adhered to six-monthly surveillance intervals (Zhang et al. 2004). Patients with viral-related liver cirrhosis have been shown to have the highest rate of compliance to surveillance compared to patients with alcohol or NASH related cirrhosis (Harris et al. 2019; Henrion et al. 2000). There are a multitude of reasons that compliance and adherence to surveillance is poor, and these can broadly be divided into healthcare and patient-related factors. First and foremost, there is a disparity in access to surveillance between different countries and populations. In many settings, cirrhosis and liver disease may be managed in a primary care setting rather than under specialist hepatology care. Evidence suggests that patients are less likely to be referred for regular surveillance screening the in primary care setting than if they are cared for in secondary care (Davila et al. 2010). Qualitative survey data from primary care providers suggests that reasons for this disparity include a lack of awareness of up to date surveillance guidance, difficulty communicating with patients about surveillance, in addition to the breadth and volume of primary care workload making HCC surveillance less of priority compared to other health conditions(Guss et al. 2018). Not all geographical areas will have access to specialist hepatologists or gastroenterologists however, in countries whereby these services are available, it is important to refer cirrhotic patients to improve continuity and consistent surveillance (Goldberg et al. 2016). Naturally, underdiagnosis of liver disease also results in lower rates of surveillance, of all etiologies NASH-related cirrhosis most frequently goes undiagnosed which poses a significant problem with the growing number of patients with metabolic disease globally (Zhai et al. 2021).

Evidence suggests that HCC disproportionately affects individuals from low socio-economic backgrounds and those from ethnic minority backgrounds. A retrospective cohort study of 904 patients with cirrhosis found that only 13% of all patients received annual surveillance and only 2% biannual surveillance with the lowest rates in African-American individuals and uninsured patients in the US (Singal et al. 2015), other studies have shown a similar pattern with the poorest uptake rates among African-American patients (Artinyan et al. 2010; Davila et al. 2010). Clinical factors shown to be positive predictors of surveillance adherence include presentation to hospital with decompensation of liver disease and if patients have a co-morbidity associated with metabolic disease (Goldberg et al. 2016). Patient attitudes and beliefs also have an impact on HCC surveillance, misconceptions include the belief that abstaining from alcohol and eating a healthy diet limits the need for surveillance, as well as being asymptomatic or having a normal physical examination (Farvardin et al. 2017). Other practical barriers include distance from surveillance centers, lack of transportation, and difficulty with scheduling appointments. Furthermore, patients affected by alcoholism and drug dependence are less likely to be able to engage with healthcare services and consequently have poorer rates of surveillance (Farvardin et al. 2017).

It is essential that healthcare professionals continue to educate patients on the importance of surveillance and practice a patient-centered approach to healthcare. By involving patients at every step of the decision-making process, they are more likely to feel empowered and take ownership of their health. Ultimately, the aim is to raise awareness, support patients with adherence to surveillance in order to diagnose HCC early and ultimately improve patient outcomes.

Biomarkers

Biomarkers are measurable biological substances which can be used as correlates for disease. In HCC, they serve an important role in early diagnosis, prognosis, and treatment selection. In particular, early detection of curable HCC through surveillance of high-risk liver cirrhosis patients is essential to improve patient survival. Several serum biomarkers have been studied. However, few HCC biomarkers fulfill the standardized biomarker validation criteria (Pepe et al. 2001), due to a lack of large prospective longitudinal studies. Serum protein biomarkers are the most well studied, with alpha-fetoprotein (AFP) the only to undergo stage five validation (Tayob et al. 2019). Other serum protein biomarkers including AFP-L3 and des-gamma-carboxy prothrombin (DCP) have demonstrated promise but lacked sufficient validation for widespread clinical use. The advancement in high-throughput sequencing has led to the development of promising genomic markers, including MicroRNAs (miRNA) (Zhang et al. 2017) and cell-free DNA (cfDNA) (Jiao et al. 2018). This chapter will explore the main biomarkers in early diagnosis, prognosis and treatment of HCC.

Alpha-Fetoprotein (AFP)

Normal Physiology and Pathophysiology

AFP is the most widely used biomarker for HCC surveillance and prognosis. AFP is a 70kD glycoprotein, with structural similarity to serum albumin (Deutsch 1991), with the AFP gene located on chromosome 4 (Lazarevich 2000). It was first identified in fetal serum in 1956 (Bergstrand and Czar 1956) and is produced by the yolk sac during the first trimester of pregnancy, and subsequently the fetal liver after yolk sac regression. It serves as the key serum protein for transportation of ligands in the fetal bloodstream (Mizejewski 2001). After birth, AFP levels regress and remain low during normal healthy lifespan, with serum albumin becoming the main serum protein. Elevated levels of AFP were first identified in patients with HCC in 1964 (Tatarinov 1964), and are seen in 60% of cases (Trevisani et al. 2001). Elevated levels are also seen in acute and chronic viral hepatitis (Abdoul et al. 2008; Kew et al. 1973), gonadal (Talerman et al. 1980) and gastric (Lu et al. 2021) tumors and pregnancy (Mizejewski 2003). The mechanism for overexpression of the AFP gene in HCC is not fully understood, but appears to be due to epigenetic silencing of suppressors at the gene promoting region (Shen et al. 2008). Though AFP correlates with specific molecular subclasses of HCC (Hoshida et al. 2009), its role carcinogenesis and proliferation is not well established. In clinical practice, the main utility of AFP is as a biomarker in surveillance, prognosis, and disease monitoring of HCC.

Surveillance in Liver Cirrhosis

AFP's role as a biomarker for HCC surveillance in patients with liver cirrhosis has been subject to debate. Using a cut-off value of 20 ng/mL, serum AFP achieved a maximal sensitivity of 60% for HCC, compared to higher cut-off values (Trevisani et al. 2001). AFP showed a high specificity of 90.6% at this level. In a population with a 5% prevalence of HCC, this equated to a positive predictive value (PPV) of only 25%, with a negative predictive value (NPV) of 90%, demonstrating the value of AFP in excluding HCC, but limitation in detecting HCC. Furthermore, AFP missed over half of early and small HCCs, with non-elevated levels seen in 52% of HCCs less than 3cm and 53.5% of early HCCs (Farinati et al. 2006). Due to its poor sensitivity, AFP used on its own appears to have a limited role in surveillance. However, AFP shows higher utility when used as an adjunct to ultrasound surveillance. A meta-analysis of 32 studies demonstrated ultrasound alone had a lower sensitivity than ultrasound plus AFP in detecting early (Relative risk 0.88; 95% Confidence Interval, 0.83–0.93) and all (Relative risk 0.81; 95% Confidence Interval, 0.71–0.93) (Tzartzeva et al. 2018). The authors did note a decrease in specificity with the addition of AFP to ultrasound (92%, 95%CI 85%–96% vs. 84%, 95%CI 77%–89%).

Due to the limited evidence and clear clinical benefit seen from these studies, both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) remain equivocal on the role of AFP in surveillance, and do not actively endorse its use in six monthly HCC surveillance of liver cirrhosis patients (Galle et al. 2018; Julie K Heimbach et al. 2018).

Prognosis of Hepatocellular Carcinoma

AFP has a significant role in prognostication in HCC. Elevated levels of AFP are associated with poor prognosis (Ikai et al. 2004; Tangkijvanich et al. 2000). Serum AFP is predictive of clinical response to various HCC treatment modalities. In liver transplant, it has a high utility in predicting cancer recurrence and post-transplant survival (Ikai et al. 2004; Zheng et al. 2008). In a large study of 12,118 patients, five-year post-transplant survival reduced from 61.5% to 41.5% for serum AFP values greater than 200 ng/mL compared to less than 20 ng/mL (Ikai et al. 2004). Multiple studies have shown values greater than 400 ng/mL is associated with significantly higher recurrence rates (Kwon et al. 2007; Toso et al. 2015; Zheng et al. 2008). Furthermore, reduction in AFP levels prior to liver transplant improves post-transplant survival (Merani et al. 2011; Ravaioli et al. 2008). As AFP demonstrates a clear predictive role in transplant outcomes, several transplant criteria models have incorporated its use. The AFP-French (Duvoux et al. 2012), Hangzhou criteria (Zheng et al. 2008) and Seoul criteria (Hong et al. 2016) all use serum AFP in the selection criteria for transplantation. However currently the EASL and AASLD society guidelines do not incorporate it's use in transplantation selection (Galle et al. 2018; Heimbach et al. 2018). AFP also predicts prognosis in non-transplant therapy. Elevated AFP is associated with increased recurrence and reduced survival in patients undergoing radiofrequency ablation (N'Kontchou et al. 2009), transcatheter arterial chemo-embolization (Takayasu et al. 2012), and systemic chemotherapy (Ando et al. 2020; Hong et al. 2021). Changes in AFP post-systemic therapy can demonstrate favorable outcomes (Kodama et al. 2019; Nakazawa et al. 2013) and early data suggests a reduction in serum levels correlates to immunotherapy response (Kuzuya et al. 2022; Sun et al. 2021). The REACH study demonstrated serum AFP levels can inform treatment decisions. Second-line use of ramucirumab showed significant survival benefit in patients with serum AFP greater than 400 ng/mL but was ineffective in patients with levels below this (Zhu et al. 2015). Subsequently a dedicated phase III trial of patients with AFP greater than 400 ng/mL demonstrated ramucirumab significantly improved overall survival and disease control rate (Zhu et al. 2019). This was the first study to implement HCC treatment based on biomarker levels.

Serum Protein Biomarkers

In addition to AFP, other serum protein biomarkers for HCC have been studied. The lens culinaris agglutinin-reactive glycosylated isoform of AFP, AFP-L3, has been used as a biomarker for early detection of HCC. AFP-L3 shows a higher specificity for HCC tissue compared to AFP and percentage fraction of AFP-L3 can be used to distinguish tumor diagnosis from underlying liver disease (Kumada et al. 2011). However, despite a high specificity, it has a low sensitivity, and AFP has shown a superior diagnostic performance than AFP-L3 fraction in detecting early HCC in cirrhosis (Kim et al. 2019; Marrero et al. 2009). Furthermore performance of the AFP-L3 assay is technically limited, with imprecise measurements seen at low (<10 ng/mL) and high (>400 ng/mL) AFP levels (Yamamoto et al. 2010). Addition of ALP-L3 to AFP has been showed to improve diagnostic performance for early stage HCC (Choi et al. 2019), but robust prospective validation still remains lacking. Des-gamma-carboxy prothrombin (DCP), (also known as prothrombin induced by vitamin K absence II (PIVKA-II)), is an aberrant protein caused by defect in vitamin K uptake in hepatocytes undergoing malignant transformation (Durazo et al. 2008). Elevated DCP levels are also seen with vitamin K deficiency, and coumarin anticoagulants (Deyashiki et al. 1989). DCP has high specificity (81–98%) but poor sensitivity (34–62%) for detection of early-stage HCC (Tsai et al. 1990). Similar to AFP-L3, there is a lack of high-quality prospective evidence to advocate its use as a biomarker on its own. However, combination of these serum biomarkers has been used in predictive clinical models. The GALAD score combines gender and age with the three protein biomarkers AFP, AFP-L3 and DCP to predict early HCC (Johnson et al. 2014). This integrated scoring system has shown a high sensitivity and specificity in detecting early stage HCC less than 3 cm in size (Berhane et al. 2016). Furthermore, it has shown utility in early detection of HCC in non-alcoholic steatohepatitis (NASH) (Best et al. 2020) cohorts, and combination with ultrasound (GALADUS) shows superior diagnostic accuracy compared to ultrasound alone (Yang et al. 2019). Future prospective multi-center studies will validate these promising findings in HCC surveillance. Other serum protein biomarkers including osteopontin (Sun et al. 2018), midkine (Vongsuvanh et al. 2016) and Dikkopf-1 (Jang et al. 2016) have all been studied in early detection of HCC, but lack longitudinal validation for routine use in clinical practice.

Genomic Biomarkers

HCC carcinogenesis is characterized by genetic DNA mutations, with epigenetic modification. Mutations seen in HCC cells can also be detected in serum and/or urine samples of patients, raising the potential for biomarker use. Genetic mutation of the TERT promoter is present in up to 60% of HCC cases (Nault et al. 2013) and is present in up to 47% of serum of patients with HCC (Jiao et al. 2018). Aberrant expression of miRNAs also plays a key role in carcinogenesis and have been studied as potential biomarkers for HCC. miRNA-21 and miRNA-199a are elevated in HCC patients (Zhang et al. 2017) and may have utility in early detection of HCC, though larger longitudinal validation is needed.

Prevention

Liver cirrhosis remains the greatest risk factor for HCC, present in up to 90% of cases (Forner et al. 2012). Primary prevention of HCC is achieved through treatment of chronic liver diseases, and prevention of progression of fibrosis. Chronic viral hepatitis remains the greatest risk factor for HCC worldwide (Akinyemiju et al. 2017). In the west, increasing rates of non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ArLD) represent growing risk factors for HCC. Genetic and autoimmune causes of chronic liver disease represent a smaller, but preventable group of HCC risk factors. This section will outline the main treatment strategies to prevent HCC for these different etiologies of liver disease.

Chronic Viral Hepatitis

Chronic viral Hepatitis B (HBV) and C (HCV) represent the largest risk factors for HCC worldwide (Akinyemiju et al. 2017). Vaccination represents the main tool for primary prevention against HBV and reduces HCC incidence. Vertical transmission through pregnancy and childbirth represents the significant risk factor for development of chronic HBV, with a risk of over 90% in children infected under the age of one year(Stevens et al. 1975). Childhood vaccine has been essential in reducing chronic HBV infections (Liang et al. 2009; Ott et al. 2012), and has reduced HCC incidence in over 80% of cases (Chang et al. 1997, 2016; Chiang et al. 2013). The World Health Organization (WHO) advocates vaccination for Hepatitis B in all new-borns, with the aim of reducing childhood prevalence of HBV to 0.1% by 2030 (World Health Organization (WHO) 2016), though implementation varies between countries globally (Muhoza et al. 2021). In those with chronic HBV, high viral load is a risk factor for HCC, in addition to presence of underlying liver fibrosis (Chen et al. 2006). Anti-viral treatment is associated with a reduced incidence of HCC (Singal et al. 2013; Wang et al. 2017) and there is a low threshold to start treatment with antiviral therapy agents including tenofovir and entecavir for patients with evidence of high HBV viral load, liver inflammation, or previous family history of HCC (Galle et al. 2018). For HCV there is no clinically available vaccine. However, reduction risk factors for blood-borne viral transmission should be implemented. This includes viral screening of all donor blood products (Roth et al. 2002) and implementation of safe needle-exchange programs for intravenous drug users (Kåberg et al. 2020). Treatment of chronic HCV has been revolutionized by direct acting agents (DAAs). Protease inhibitors have been shown to achieve a sustained virological response (SVR) of up to 90% for the majority of HCV genotypes (Falade-Nwulia et al. 2017; Pawlotsky 2014). There is limited data to suggested DAA associated SVR is associated with reduce incidence of HCC (Ioannou et al. 2018), though post-treatment cancer surveillance is required in patients with underlying cirrhosis (Roche et al. 2018).

Non-Alcoholic Fatty Liver Disease (NAFLD)

The rising rates of obesity worldwide has been associated with increased rates of NAFLD (Fan et al. 2017; Younossi et al. 2016) and NAFLD-related HCC (Dyson et al. 2014; Wong et al. 2014). Non-alcoholic steatohepatitis (NASH) can cause HCC in the absence of cirrhosis in 15–63% of cases (Kanwal et al. 2018; Pais et al. 2017; Pinyopornpanish et al. 2021; Piscaglia et al. 2016). Lifestyle and medical treatment of underlying NASH and NAFLD is therefore important for HCC prevention. Healthy lifestyle factors, including normal body mass index and a Mediterranean diet, are associated with a lower risk of HCC (Luu et al. 2021). Furthermore, increased physical activity (Baumeister et al. 2019) and weight reduction have shown suggestive negative associations with HCC (Kwak et al. 2020). Several population studies have demonstrated medical therapy with metformin is associated with a reduction in HCC (Singh et al. 2013; Zhang et al. 2012), though prospective randomized controlled trials are lacking. Similarly, statins have also been associated with a lower risk of HCC (Facciorusso et al. 2020; Islam et al. 2020), with prospective randomized clinical trials ongoing (Lange et al. 2021). Newer NASH targeted therapies, including vitamin E (Abdel-Maboud et al. 2020) and obeticholic acid (Ratziu et al. 2019) may represent potential mechanisms for reducing future risk of HCC.

Alcohol-related Liver Disease (ArLD) and Other Chronic Liver Diseases

ArLD remains a significant preventable risk factor for HCC (Donato et al. 2002). Due to limited medical therapy, preventative therapy relies on reduction in high-risk intake of alcohol and requires psychological and sociological strategies at small and large community levels. Public health strategies including alcohol taxation and increased pricing policies can reduce the burden of ArLD, but vary greatly different countries (Ventura-Cots et al. 2019). Medical therapies for autoimmune liver diseases such as autoimmune hepatitis (Choi and Choi et al. 2019; Vaz et al. 2020) and primary biliary cirrhosis (Kuiper et al. 2010; Trivedi et al. 2016) are important for reducing inflammation, progression to cirrhosis, and HCC. Similarly, management of genetic conditions including hereditary haemochromatosis and Wilson's disease can reduce risk of progression of cirrhosis and HCC (Elmberg et al. 2003; Reyes 2008). Venesection, iron chelation and genetic screening of relatives are all effective treatment strategies in haemochromatosis (Niederau et al. 1996).

Aspirin

The chemopreventative role of aspirin has been studied in multiple cancers. Through cyclooxygenase-1 (COX-1) and -2 (COX-2) inhibition, aspirin exhibits antiplatelet and anti-inflammatory effects, mediating cancer prevention. A recent meta-analysis of all observational studies on aspirin for the prevention of digestive tract cancers estimated the pooled relative risk (RR) of cancer for regular aspirin use versus non-use using random effects models (Bosetti et al. 2020). In this study, regular aspirin use was associated with a reduced risk of colorectal cancer (RR 0.73, 95% CI 0.69–0.78, 45 studies), squamous-cell esophageal cancer (RR 0.67, 95% CI 0.57–0.79, 13 studies), adenocarcinoma of the esophagus and gastric cardia (RR 0.61, 95% CI 0.49 – 0.77, 10 studies), stomach cancer (RR 0.64, 95% CI 0.51–0.82, 14 studies), hepato-biliary tract cancer (RR 0.62, 95% CI 0.440–0.86, five studies), and pancreatic cancer (RR 0.78, 95% CI 0.68–0.89, 15 studies).While the strongest evidence for cancer prevention is seen in colorectal cancer (Burn et al. 2020; Ishikawa et al. 2021), there is growing evidence for aspirin's role in prevention of HCC in both general and high-risk populations. Long-term data from the Nurses' Health Study (Simon et al. 2018) and the National Cohort Study of Korean Adults (Hwang et al. 2018) demonstrate aspirin reduced HCC risk in patients with and without underlying liver disease. Aspirin use in patients with HBV is associated with a reduction in HCC incidence of 29–56% in Korean and Taiwanese populations (Lee et al. 2017, 2019). Similar risk reduction with low-dose aspirin use was seen in patients with chronic HCV (Lee et al. 2020; Liao et al. 2020; Simon et al. 2020) and alcohol associated liver disease (Shin et al. 2020). Aspirin use can reduce the progression to fibrosis in NAFLD (Simon et al. 2019) and has been associated with up to a 50% reduction in HCC in prospective population studies (Simon et al. 2018). The biological plausibility of aspirin reducing the risk of hepatobiliary cancer, in parallel to the published epidemiological data, has been extensively reviewed and includes its ability to: inhibit COX-2 in dysplastic tissue (which promotes inflammation and cell proliferation), inhibit activation of nuclear factor kB, prevent platelet aggregation (which may slow metastatic spread), modulate Wnt signaling via both COX-dependent and COX-independent pathways, upregulate tumor suppressor genes and stabilize DNA mismatch-repair proteins (Shen and Shen 2021). Though observational studies show promising outcomes, there is a need for high-quality prospective randomized control data before aspirin can be used in routine clinical practice. Given the increased bleeding risk in patients with chronic liver disease, robust clinical trial data is needed to evaluate the full safety and efficacy profile of aspirin in this cohort.

Key Take Home Messages

- Imaging surveillance of high-risk patients with chronic liver disease and chronic hepatitis B reduces hepatocellular carcinoma related mortality.
- Arterial enhancement followed by washout during the portal venous and delayed acquisition phase on computer topography and magnetic resonance imaging allow for radiological diagnosis of hepatocellular carcinoma without the need for tissue biopsy.
- Primary prevention of chronic hepatitis B through childhood vaccination and antiviral therapy for chronic hepatitis B reduces hepatocellular carcinoma and mortality.
- Alpha-fetoprotein has utility in predicting disease recurrence and survival post liver transplant and is incorporated in transplant selection criteria.
- Surveillance of hepatocellular carcinoma is less than 20%, with better access to secondary care essential for improving rates.

Knowledge Gaps

- The utility of serum biomarkers in hepatocellular carcinoma surveillance remains unclear. Further high quality randomized prospective evaluation of biomarkers in combination with imaging for surveillance is needed.
- The optimal imaging modality for surveillance remains unclear, with computer topography, magnetic resonance imaging, ultrasound, and contrast-enhanced ultrasound demonstrating varied clinical and economic advantages. Longer term head-to-head randomized clinical trials are needed to determine the optimal surveillance strategies.
- Primary and secondary prevention strategies and therapeutics are needed to tackle the rising incidence of non-alcoholic fatty liver disease and limit the impact on rates of hepatocellular carcinoma.
- Alpha-fetoprotein demonstrates promise for guiding non-transplant therapeutic selection, but further studies are needed for its utility in precision medicine.
- “Is chemoprevention possible with aspirin or other medications?”

Trusted Websites for Further Reading

https://www.mdanderson.org/research/departments-labs-institutes/spores/hepatocellular-carcinoma-spore/investigators-and-staff.html

https://mayoclinic.pure.elsevier.com/en/publications/prevention-of-hepatocellular-carcinoma-progress-and-challenges

References

Abdel-Maboud, M., Menshawy, A., Menshawy, E. et al. (2020). The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Therap Adv Gastroenterol* 13: 175628482097491. doi: 10.1177/1756284820974917.

Abdoul, H., Mallet, V., Pol, S. et al. (2008). Serum alpha-fetoprotein predicts treatment outcome in chronic hepatitis C patients regardless of HCV genotype. *PloS one* 3 (6): e2391. doi: 10.1371/journal.pone.0002391.

Akinyemiju, T., Abera, S., Ahmed, M. et al. (2017). The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. *JAMA Oncol* 3 (12): 1683. doi: 10.1001/jamaoncol.2017.3055.

Andersson, K.L., Salomon, J.A., Goldie, S.J. et al. (2008). Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 6 (12): 1418–1424. doi: 10.1016/j.cgh.2008.08.005.

Ando, Y., Kawaoka, T., Suehiro, Y. et al. (2020). Analysis of post-progression survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib. *Oncology* 98 (11): 787–797. doi: 10.1159/000509387.

Andreana, L., Isgrò, G., Pleguezuelo, M. et al. (2009). Surveillance and diagnosis of hepatocellular carcinoma in patients with cirrhosis. *World J Hepatol* 1 (1): 48–61. doi: 10.4254/wjh.v1.i1.48.

Andreassen, C.N., Alsner, J., and Overgaard, J. (2002). Does variability in normal tissue reactions after radiotherapy have a genetic basis–where and how to look for it? *Radiother Oncol : J Eur Soc Ther Radiol Oncol* 64 (2): 131–140. doi: 10.1016/s0167-8140(02)00154-8.

Angermayr, B., Cejna, M., Karnel, F. et al. (2003). Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. *Gut* 52 (6): 879–885. doi: 10.1136/gut.52.6.879.

Anugwom, C.M., Allaire, M., Akbar, S.M.F. et al. (2021). Hepatitis B-related hepatocellular carcinoma: surveillance strategy directed by immune-epidemiology. *Hepatoma Res* doi: 10.20517/2394-5079.2021.06.

Arroyo, V., Moreau, R., Kamath, P.S. et al. (2016). Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers* 2: 16041. doi: 10.1038/nrdp.2016.41.

Artinyan, A., Mailey, B., Sanchez-Luege, N. et al. (2010). Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. *Cancer* 116 (5): 1367–1377. doi: 10.1002/cncr.24817.

Barbara, L., Benzi, G., Gaiani, S. et al. (1992). Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. *Hepatology* 16 (1): 132–137. doi: 10.1002/hep.1840160122.

Bartolotta, T.V., Taibbi, A., Midiri, M. et al. (2019). Contrast-enhanced ultrasound of hepatocellular carcinoma: where do we stand?. *Ultrasonography* 38 (3): 200–214. doi: 10.14366/usg.18060.

Baumeister, S.E., Leitzmann, M.F., Linseisen, J. et al. (2019). Physical activity and the risk of liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis. *J Natl Cancer Inst* 111 (11): 1142–1151. doi: 10.1093/jnci/djz111.

Bergstrand, C.G. and Czar, B. (1956). Demonstration of a new protein fraction in serum from the human fetus. *Scand J Clin Lab Invest* 8 (2): 174. doi: 10.3109/00365515609049266.

Berhane, S., Toyoda, H., Tada, T. et al. (2016). Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. *Clin Gastroenterol Hepatol : Off Clin Pract J Am Gastroenterol Ass* 14 (6): 875–886.e6. doi: 10.1016/j.cgh.2015.12.042.

Berzigotti, A., Tsochatzis, E., Boursier, J. et al. (2021). EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. *J Hepatol* 75 (3): 659–689. doi: 10.1016/j.jhep.2021.05.025.

Best, J., Bechmann, L.P., Sowa, J.-P. et al. (2020). GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol : Off Clin Pract J Am Gastroenterol Ass* 18 (3): 728–735.e4. doi: 10.1016/j.cgh.2019.11.012.

Blechacz, B. (2017). Cholangiocarcinoma: current knowledge and new developments. *Gut Liver* 11 (1): 13–26. doi: 10.5009/gnl15568.

Bosetti, C., Santucci, C., Gallus, S. et al. (2020). Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol : Off J Eur Soc Med Oncol* 31 (5): 558–568. doi: 10.1016/j.annonc.2020.02.012.

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68 (6): 394–424. doi: 10.3322/caac.21492.

Bruix, J. and Sherman, M. and American Association for the Study of Liver Diseases. (2011). Management of hepatocellular carcinoma: an update. *Hepatology (Baltimore, Md)* 53 (3): 1020–1022. doi: 10.1002/hep.24199.

Burn, J., Sheth, H., Elliott, F. et al. (2020). Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet (London, England)* 395 (10240): 1855–1863. doi: 10.1016/S0140-6736(20)30366-4.

Caruso, S., O'Brien, D.R., Cleary, S.P. et al. (2021). Genetics of hepatocellular carcinoma: approaches to explore molecular diversity. *Hepatology* 73 (S1): 14–26. doi: 10.1002/hep.31394.

Chang, M.H., Chen, C.J., Lai, M.S. et al. (1997). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 336 (26): 1855–1859. doi: 10.1056/NEJM199706263362602.

Chang, M.-H., You, S.-L., Chen, C.-J. et al. (2016). Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology* 151 (3): 472–480.e1. doi: 10.1053/j.gastro.2016.05.048.

Chang, S., Kim, S.H., Lim, H.K. et al. (2008). Needle tract implantation after percutaneous interventional procedures in hepatocellular carcinomas: lessons learned from a 10-year experience. *Korean J Radiol* 9 (3): 268. doi: 10.3348/kjr.2008.9.3.268.

Chen, C.-J., Yang, H.-I., Su, J. et al. (2006). Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 295 (1): 65–73. doi: 10.1001/jama.295.1.65.

Chernyak, V., Fowler, K.J., Kamaya, A. et al. (2018). Liver Imaging Reporting and Data System (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. *Radiology* 289 (3): 816–830. doi: 10.1148/radiol.2018181494.

Chiang, C.-J., Yang, Y.-W., You, S.-L. et al. (2013). Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA* 310 (9): 974. doi: 10.1001/jama.2013.276701.

Chidambaranathan-Reghupaty, S., Fisher, P.B., and Sarkar, D. (2021). Hepatocellular carcinoma (HCC): epidemiology, etiology and molecular classification. *Adv Cancer Res* 149: 1–61. doi: 10.1016/bs.acr.2020.10.001.

Childs, A., Zakeri, N., Ma, Y.T. et al. (2021). Biopsy for advanced hepatocellular carcinoma: results of a multicentre UK audit. *Br J Cancer* 125 (10): 1350–1355. doi: 10.1038/s41416-021-01535-2.

Choi, J., Choi, G.H., Lee, D. et al. (2019). Long-term clinical outcomes in patients with autoimmune hepatitis according to treatment response in Asian country. *Liver Int : Off J Int Ass Study Liver* 39 (5): 985–994. doi: 10.1111/liv.14082.

Choi, J., Kim, G.-A., Han, S.et al. (2019). Longitudinal assessment of three serum biomarkers to detect very early-stage hepatocellular carcinoma. *Hepatology (Baltimore, Md.)* 69 (5): 1983–1994. doi: 10.1002/hep.30233.

Choi, J.-Y., Lee, J.-M., and Sirlin, C.B. (2014). CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects. *Radiology* 272 (3): 635–654. doi: 10.1148/radiol.14132361.

Cooper, G.S., Bellamy, P., Dawson, N.V. et al. (1997). A prognostic model for patients with end-stage liver disease. *Gastroenterology* 113 (4): 1278–1288. doi: 10.1053/gast.1997.v113.pm9322523.

D'Amico, G., Garcia-Tsao, G., and Pagliaro, L. (2006). Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 44 (1): 217–231. doi: 10.1016/j.jhep.2005.10.013.

Davila, J.A., Morgan, R.O., Richardson, P.A. et al. (2010). Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology* 52 (1): 132–141. doi: 10.1002/hep.23615.

Deutsch, H.F. (1991). Chemistry and biology of alpha-fetoprotein. *Adv Cancer Res* 56: 253–312. doi: 10.1016/s0065-230x(08)60483-2.

Deyashiki, Y., Nishioka, Y., Takahashi, K. et al. (1989). Evaluation of des-gamma-carboxy prothrombin as a marker protein of hepatocellular carcinoma. *Cancer* 64 (12): 2546–2551. doi: 10.1002/1097-0142(19891215)64:12<2546::aid-cncr2820641223>3.0.co;2-q.

Donato, F., Tagger, A., Gelatti, U. et al. (2002). Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* 155 (4): 323–331. doi: 10.1093/aje/155.4.323.

Durazo, F.A., Blatt, L.M., Corey, W.G. et al. (2008). Des-gamma-carboxyprothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. *J Gastroenterol Hepatol* 23 (10): 1541–1548. doi: 10.1111/j.1440-1746.2008.05395.x.

Duvoux, C., Roudot-Thoraval, F., Decaens, T. et al. (2012). Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria.

Gastroenterology 143 (4): 986–94.e3. quiz e14-5. doi: 10.1053/j.gastro.2012.05.052.

Dvorak, H.F. (2002). Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *J Clin Oncol : Off J Am Soc Clin Oncol* 20 (21): 4368–4380. doi: 10.1200/JCO.2002.10.088.

Dyson, J., Jaques, B., Chattopadyhay, D. et al. (2014). Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. *J Hepatol* 60 (1): 110–117. doi: 10.1016/j.jhep.2013.08.011.

Elmberg, M., Hultcrantz, R., Ekbom, A. et al. (2003). Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 125 (6): 1733–1741. doi: 10.1053/j.gastro.2003.09.035.

El-Serag, H.B. and Rudolph, K.L. (2007). Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 132 (7): 2557–2576. doi: 10.1053/j.gastro.2007.04.061.

Esfeh, J.M., Hajifathalian, K., and Ansari-Gilani, K. (2020). Sensitivity of ultrasound in detecting hepatocellular carcinoma in obese patients compared to explant pathology as the gold standard. *Clin Mol Hepatol* 26 (1): 54–59. doi: 10.3350/cmh.2019.0039.

Facciorusso, A., Abd El Aziz, M.A., Singh, S. et al. (2020). Statin use decreases the incidence of hepatocellular carcinoma: an updated meta-analysis. *Cancers* 12 (4): doi: 10.3390/cancers12040874.

Falade-Nwulia, O., Suarez-Cuervo, C., Nelson, D.R. et al. (2017). Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. *Ann Intern Med* 166 (9): 637–648. doi: 10.7326/M16-2575.

Fan, J.-G., Kim, S.-U., and Wong, V.W.-S. (2017). New trends on obesity and NAFLD in Asia. *J Hepatol* 67 (4): 862–873. doi: 10.1016/j.jhep.2017.06.003.

Farinati, F., Marino, D., De Giorgio, M. et al. (2006). Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither? *Am. J. Gastroenterol* 101 (3): 524–532. doi: 10.1111/j.1572-0241.2006.00443.x.

Farvardin, S., Patel, J., Khambaty, M. et al. (2017). Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. *Hepatology (Baltimore, Md.)* 65 (3): 875–884. doi: 10.1002/hep.28770.

Fitzmorris, P. and Singal, A.K. (2015). Surveillance and diagnosis of hepatocellular carcinoma. *Gastroenterol hepatol* 11 (1): 38–46. Available at, http://www.ncbi.nlm.nih.gov/pubmed/27099571. (accessed on 14th March 2023).

Foerster, F. and Galle, P.R. (2019). Comparison of the current international guidelines on the management of HCC. *JHEP Rep: Innovation in Hepatology* 1 (2): 114–119. doi: 10.1016/j.jhepr.2019.04.005.

Forner, A., Llovet, J.M., and Bruix, J. et al. (2008). Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology (Baltimore, Md)* 47 (1): 97–104. doi: 10.1002/hep.21966.

Forner, A., Llovet, J.M., and Bruix, J. (2012). Hepatocellular carcinoma. *Lancet (London, England)* 379 (9822): 1245–1255. doi: 10.1016/S0140-6736(11)61347-0.

Galle, P.R., Forner, A., Llovet, J.M. et al. (2018). EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 69 (1): 182–236. doi: 10.1016/j.jhep.2018.03.019.

Ginés, P., Quintero, E., Arroyo, V. et al. (1987). Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 7 (1): 122–128. doi: 10.1002/hep.1840070124.

Goldberg, D.S., Valderrama, A., Kamalakar, R. et al. (2016). Hepatocellular carcinoma surveillance among cirrhotic patients with commercial health insurance. *J Clin Gastroenterol* 50 (3): 258–265. doi: 10.1097/MCG.0000000000000411.

Gotink, K.J. and Verheul, H.M.W. (2010). Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action? *Angiogenesis* 13 (1): 1–14. doi: 10.1007/s10456-009-9160-6.

Grover, V.P.B., Tognarelli, J.M., Crossey, M.M.E. et al. (2015). Magnetic resonance imaging: principles and techniques: lessons for clinicians. *J Clin Exp Hepatol* 5 (3): 246–255. doi: 10.1016/j.jceh.2015.08.001.

Guichard, C., Amaddeo, G., Imbeaud, S. et al. (2012). Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. *Nat Genet* 44 (6): 694–698. doi: 10.1038/ng.2256.

Guss, D., Sherigar, J., and Mohanty, S.R. (2018). Missed diagnosis of liver cirrhosis leads to disparities in care for older patients. *Gastroenterol Res* 11 (5): 333–339. doi: 10.14740/gr1074w.

Harris, P.S., Hansen, R.M., Gray, M.E. et al. (2019). Hepatocellular carcinoma surveillance: an evidence-based approach. *World J Gastroenterol* 25 (13): 1550–1559. doi: 10.3748/wjg.v25.i13.1550.

Hassan, M.M., Kaseb, A., Etzel, C.J. et al. (2013). Genetic variation in the PNPLA3 gene and hepatocellular carcinoma in USA: risk and prognosis prediction. *Mol Carcinog* 52 (S1): 139–147. doi: 10.1002/mc.22057.

Heimbach, J.K., Kulik, L.M., Finn, R.S. et al. (2018). AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology (Baltimore, Md.)* 67 (1): 358–380. doi: 10.1002/hep.29086.

Heleno, B., Thomsen, M.F., Rodrigues, D.S. et al. (2013 sep16). Quantification of harms in cancer screening trials: literature review. *BMJ* 347 (1): f5334–f5334. doi: 10.1136/bmj.f5334.

Henrion, J., Libon, E., De Maeght, S. et al. (2000). Surveillance for hepatocellular carcinoma: compliance and results according to the aetiology of cirrhosis in a cohort of 141 patients. *Acta Gastro-Enterol Belg* 63 (1): 5–9. Available at, http://www.ncbi.nlm.nih.gov/pubmed/10907311.

Hong, S.K., Lee, K.-W., Kim, H.-S. et al. (2016). Living donor liver transplantation for hepatocellular carcinoma in Seoul national university. *Hepatobiliary Surg* 5 (6): 453–460. doi: 10.21037/hbsn.2016.08.07.

Hong, Y.M., Yoon, K.T., and Cho, M. (2021). Systemic immune-inflammation index predicts prognosis of sequential therapy with sorafenib and regorafenib in hepatocellular carcinoma. *BMC Cancer* 21 (1): 569. doi: 10.1186/s12885-021-08124-9.

Hoshida, Y., Nijman, S.M.B., Kobayashi, M. et al. (2009). Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. *Cancer Res* 69 (18): 7385–7392. doi: 10.1158/0008-5472.CAN-09-1089.

Hwang, I.C., Chang, J., Kim, K. et al. (2018). Aspirin use and risk of hepatocellular carcinoma in a national cohort study of Korean adults. *Sci Rep* 8 (1): 4968. doi: 10.1038/s41598-018-23343-0.

Iannacone, M. and Guidotti, L.G. (2022). Immunobiology and pathogenesis of hepatitis B virus infection. *Nat Rev Immunol* 22 (1): 19–32. doi: 10.1038/s41577-021-00549-4.

Ikai, I., Arii, S., Kojiro, M. et al. (2004). Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. *Cancer* 101 (4): 796–802. doi: 10.1002/cncr.20426.

Ioannou, G.N., Green, P.K., and Berry, K. (2018). HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol* 68 (1): 25–32. doi: 10.1016/j.jhep.2017.08.030.

Ishikawa, H., Mutoh, M., Sato, Y. et al. (2021). Chemoprevention with low-dose aspirin, mesalazine, or both in patients with familial adenomatous polyposis without previous colectomy (J-FAPP study IV): a multicentre, double-blind, randomised, two-by-two factorial design trial. *Lancet Gastroenterol Hepatol* 6 (6): 474–481. doi: 10.1016/S2468-1253(21)00018-2.

Islam, M.M., Poly, T.N., Walther, B.A. et al. (2020). Statin use and the risk of hepatocellular carcinoma: a meta-analysis of observational studies. *Cancers* 12 (3): doi: 10.3390/cancers12030671.

Jang, E.S., Jeong, S.-H., Kim, J.-W. et al. (2016). Diagnostic performance of alpha-fetoprotein, protein induced by vitamin k absence, osteopontin, dickkopf-1 and its combinations for hepatocellular carcinoma. *PloS one* 11 (3): e0151069. doi: 10.1371/journal.pone.0151069.

Jiao, J., Watt, G.P., Stevenson, H.L. et al. (2018). Telomerase reverse transcriptase mutations in plasma DNA in patients with hepatocellular carcinoma or cirrhosis: prevalence and risk factors. *Hepatol Commun* 2 (6): 718–731. doi: 10.1002/hep4.1187.

Johnson, P.J., Pirrie, S.J., Cox, T.F. et al. (2014). The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. *Cancer Epidemiol Biomarkers Prev: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 23 (1): 144–153. doi: 10.1158/1055-9965.EPI-13-0870.

Kåberg, M., Karlsson, N., Discacciati, A. et al. (2020). Significant decrease in injection risk behaviours among participants in a needle exchange programme. *Infect Dis (London, England)* 52 (5): 336–346. doi: 10.1080/23744235.2020.1727002.

Kanwal, F., Kramer, J.R., Mapakshi, S. et al. (2018). Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 155 (6): 1828–1837.e2. doi: 10.1053/j.gastro.2018.08.024.

Kanwal, F. and Singal, A.G. (2019). Surveillance for hepatocellular carcinoma: current best practice and future direction. *Gastroenterology* 157 (1): 54–64. doi: 10.1053/j.gastro.2019.02.049.

Kew, M.C., Purves, L.R., and Bersohn, I. (1973). Serum alpha-fetoprotein levels in acute viral hepatitis. *Gut* 14 (12): 939–942. doi: 10.1136/gut.14.12.939.

Kim, J., Kang, W., Sinn, D.H. et al. (2020). Substantial risk of recurrence even after 5 recurrence-free years in early-stage hepatocellular carcinoma patients. *Clin Mol Hepatol* 26 (4): 516–528. doi: 10.3350/cmh.2020.0016.

Kim, S., Shin, J., Kim, D.-Y. et al. (2019). Radiomics on gadoxetic acid-enhanced magnetic resonance imaging for prediction of postoperative early and late recurrence of single hepatocellular carcinoma. *Clin Cancer Res: Off J Am Ass Cancer Res* 25 (13): 3847–3855. doi: 10.1158/1078-0432.CCR-18-2861.

Kim, T.K., Noh, S.Y., Wilson, S.R. et al. (2017). Contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LI-RADS) 2017 – a review of important differences compared to the CT/MRI system. *Clin Mol Hepatol* 23 (4): 280–289. doi: 10.3350/cmh.2017.0037.

Kodama, K., Kawaoka, T., Namba, M. et al. (2019). Correlation between early tumor marker response and imaging response in patients with advanced hepatocellular carcinoma treated with lenvatinib. *Oncology* 97 (2): 75–81. doi: 10.1159/000499715.

Kono, H. and Rock, K.L. (2008). How dying cells alert the immune system to danger. *Nat Rev Immunol* 8 (4): 279–289. doi: 10.1038/nri2215.

Kovac, J.D., Ivanovic, A., Milovanovic, T. et al. (2021). An overview of hepatocellular carcinoma with atypical enhancement pattern: spectrum of magnetic resonance imaging findings with pathologic correlation. *Radiol Oncol* 55 (2): 130–143. doi: 10.2478/raon-2021-0004.

Kudo, M. (2012). Japan's successful model of nationwide hepatocellular carcinoma surveillance highlighting the urgent need for global surveillance. *Liver Cancer* 1 (3–4): 141–143. doi: 10.1159/000342749.

Kuiper, E.M.M., Hansen, B.E., Adang, R.P.R. et al. (2010). Relatively high risk for hepatocellular carcinoma in patients with primary biliary cirrhosis not responding to ursodeoxycholic acid. *Eur J Gastroenterol Hepatol* 22 (12): 1495–1502. doi: 10.1097/MEG.0b013e32834059e7.

Kumada, T., Toyoda, H., Kiriyama, S. et al. (2011). Predictive value of tumor markers for hepatocarcinogenesis in patients with hepatitis C virus. *J Gastroenterol* 46 (4): 536–544. doi: 10.1007/s00535-010-0349-7.

Kuzuya, T., Kawabe, N., Hashimoto, S. et al. (2022). Early changes in alpha-fetoprotein are a useful predictor of efficacy of atezolizumab plus bevacizumab treatment in patients with advanced hepatocellular carcinoma. *Oncology* 100 (1): 12–21. doi: 10.1159/000519448.

Kwak, M., Mehaffey, J.H., Hawkins, R.B. et al. (2020). Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: a propensity matched analysis. *Am J Surg* 219 (3): 504–507. doi: 10.1016/j.amjsurg.2019.09.006.

Kwon, C.H.D., Kim, D.J., Han, Y.S. et al. (2007). HCC in living donor liver transplantation: can we expand the milan criteria? *Dig Dis* 25 (4): 313–319. doi: 10.1159/000106911.

Lange, N.F., Radu, P., and Dufour, J.-F. (2021). Prevention of NAFLD-associated HCC: role of lifestyle and chemoprevention. *J Hepatol* 75 (5): 1217–1227. doi: 10.1016/j.jhep.2021.07.025.

Lazarevich, N.L. (2000). Molecular mechanisms of alpha-fetoprotein gene expression. *Biochemistry Biokhimiia* 65 (1): 117–133. Available at http://www.ncbi.nlm.nih.gov/pubmed/10702646.

Lee, M., Chung, G.E., Lee, J.-H. et al. (2017). Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment. *Hepatology (Baltimore, Md.)* 66 (5): 1556–1569. doi: 10.1002/hep.29318.

Lee, T.-Y., Hsu, Y.-C., Tseng, H.-C. et al. (2019). Association of daily aspirin therapy with risk of hepatocellular carcinoma in patients with chronic hepatitis B. *JAMA Intern Med* 179 (5): 633–640. doi: 10.1001/jamainternmed.2018.8342.

Lee, T.-Y ., Hsu, Y.-C., Tseng, H.-C. et al. (2020). Association of daily aspirin therapy with hepatocellular carcinoma risk in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol: Off Clin Pract J Am Gastroenterol Ass* 18 (12): 2784–2792.e7. doi: 10.1016/j.cgh.2020.04.036.

Lee, Y., Wang, J.J., Zhu, Y. et al. (2021). Diagnostic criteria and LI-RADS for hepatocellular carcinoma. *Clin Liver Dis* 17 (6): 409–413. doi: 10.1002/cld.1075.

Liang, X., Bi, S., Yang, W. et al. (2009). Epidemiological serosurvey of hepatitis B in China–declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 27 (47): 6550–6557. doi: 10.1016/j.vaccine.2009.08.048.

Liao, Y.-H., Hsu, R.-J., Wang, T.-H. et al. (2020). Aspirin decreases hepatocellular carcinoma risk in hepatitis C virus carriers: a nationwide cohort study. *BMC Gastroenterol* 20 (1): 6. doi: 10.1186/s12876-020-1158-y.

Llovet, J.M., Kelley, R.K., Villanueva, A. et al. (2021). Hepatocellular carcinoma. *Nat Rev Dis Primers* 7 (1): 6. doi: 10.1038/s41572-020-00240-3.

Lu, J., Jin, M., Zhou, X. et al. (2021). Clinicopathological and molecular characteristics of the alpha-fetoprotein-producing gastric cancer: emphasis on two major subtypes. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica*. doi: 10.1111/apm.13196.

Luu, H.N., Behari, J., Goh, G.B.-B. et al. (2021). Composite score of healthy lifestyle factors and risk of hepatocellular carcinoma: findings from a prospective cohort study. *Cancer Epidemiol Biomarkers Prev : A Publication Am Ass Cancer Res, Cosponsored by the Am Soc Prev Oncol* 30 (2): 380–387. doi: 10.1158/1055-9965.EPI-20-1201.

Lyshchik, A., Kono, Y., Dietrich, C.F. et al. (2018). Contrast-enhanced ultrasound of the liver: technical and lexicon recommendations from the ACR CEUS LI-RADS working group. *Abdom Radiol* 43 (4): 861–879. doi: 10.1007/s00261-017-1392-0.

Maeda, M., Saeki, I., Sakaida, I. et al. (2020). Complications after radiofrequency ablation for hepatocellular carcinoma: a multicenter study involving 9,411 Japanese patients. *Liver Cancer* 9 (1): 50–62. doi: 10.1159/000502744.

Marrero, J.A., Feng, Z., Wang, Y. et al. (2009). Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology* 137 (1): 110–118. doi: 10.1053/j.gastro.2009.04.005.

Marrero, J.A., Kulik, L.M., Sirlin, C.B. et al. (2018). Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. *Hepatology (Baltimore, Md.)* 68 (2): 723–750. doi: 10.1002/hep.29913.

McCabe, C., Claxton, K., and Culyer, A.J. (2008). The NICE cost-effectiveness threshold. *PharmacoEconomics* 26 (9): 733–744. doi: 10.2165/00019053-200826090-00004.

Merani, S., Majno, P., Kneteman, N.M. et al. (2011). The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. *J Hepatol* 55 (4): 814–819. doi: 10.1016/j.jhep.2010.12.040.

Mizejewski, G.J. (2001). Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants. *Exp Biol Med (Maywood, NJ)* 226 (5): 377–408. doi: 10.1177/153537020122600503.

Mizejewski, G.J. (2003). Levels of alpha-fetoprotein during pregnancy and early infancy in normal and disease states. *Obstet Gynecol Surv* 58 (12): 804–826. doi: 10.1097/01.OGX.0000099770.97668.18.

Morse, M.A., Sun, W., Kim, R. et al. (2019). The role of angiogenesis in hepatocellular carcinoma. *Clin Cancer Res* 25 (3): 912–920. doi: 10.1158/1078-0432.CCR-18-1254.

Motz, V.L., White, R., Lee, R. et al. (2021). Contrast-enhanced ultrasound for screening hepatocellular carcinoma: an implemented program at a semi-rural academic center. *Abdom Radiol* 46 (9): 4170–4177. doi: 10.1007/s00261-021-03104-w.

Moura Cunha, G., Chernyak, V., Fowler, K.J. et al. (2021). Up-to-date role of CT/MRI LI-RADS in hepatocellular carcinoma. *J Hepatocell Carcinoma* 8: 513–527. doi: 10.2147/JHC.S268288.

Muhoza, P., Danovaro-Holliday, M.C., Diallo, M.S. et al. (2021). Routine vaccination coverage - Worldwide, 2020. *MMWR Morb Mortal Wkly Rep* 70 (43): 1495–1500. doi: 10.15585/mmwr.mm7043a1.

N'Kontchou, G., Mahamoudi, A., Aout, M. et al. (2009). Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology (Baltimore, Md)* 50 (5): 1475–1483. doi: 10.1002/hep.23181.

Nahon, P. and Zucman-Rossi, J. (2012). Single nucleotide polymorphisms and risk of hepatocellular carcinoma in cirrhosis. *J Hepatol* 57 (3): 663–674. doi: 10.1016/j.jhep.2012.02.035.

Nakazawa, T., Hidaka, H., Takada, J. et al. (2013). Early increase in α-fetoprotein for predicting unfavorable clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol* 25 (6): 683–689. doi: 10.1097/MEG.0b013e32835d913b.

Nault, J.C., Mallet, M., Pilati, C. et al. (2013). High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. *Nat Commun* 4: 2218. doi: 10.1038/ncomms3218.

Nault, J.-C., Ningarhari, M., Rebouissou, S. et al. (2019). The role of telomeres and telomerase in cirrhosis and liver cancer. *Nat Rev Gastroenterol Hepatol* 16 (9): 544–558. doi: 10.1038/s41575-019-0165-3.

Niederau, C., Fischer, R., Pürschel, A. et al. (1996). Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 110 (4): 1107–1119. doi: 10.1053/gast.1996.v110.pm8613000.

Noguchi, Y., Murakami, T., Kim, T. et al. (2003). Detection of hepatocellular carcinoma: comparison of dynamic mr imaging with dynamic double arterial phase helical CT. *Am J Roentgenol* 180 (2): 455–460. doi: 10.2214/ajr.180.2.1800455.

Oleske, D.M. (2009). Screening and surveillance for promoting population health In: *Epidemiology and the Delivery of Health Care Services*, 131–150. Boston, MA: Springer US. doi: 10.1007/978-1-4419-0164-4_5.

Ott, J.J., Stevens, G.A., Groeger, J. et al. (2012). Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 30 (12): 2212–2219. doi: 10.1016/j.vaccine.2011.12.116.

Pais, R., Fartoux, L., Goumard, C. et al. (2017). Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period. *Aliment Pharmacol Ther* 46 (9): 856–863. doi: 10.1111/apt.14261.

Pawlotsky, J.-M. (2014). New hepatitis C therapies: the toolbox, strategies, and challenges. *Gastroenterology* 146 (5): 1176–1192. doi: 10.1053/j.gastro.2014.03.003.

Pelletier, A.R., Siegel, P.Z., Baptiste, M.S. et al. (2005). Revisions to chronic disease surveillance indicators, United States, 2004. *Prev Chronic Dis* 2 (3): A15. Available at http://www.ncbi.nlm.nih.gov/pubmed/15963317.

Pepe, M.S., Etzioni, R., Feng, Z. et al. (2001). Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 93 (14): 1054–1061. doi: 10.1093/jnci/93.14.1054.

Pinyopornpanish, K., Khoudari, G., Saleh, M.A. et al. (2021). Hepatocellular carcinoma in nonalcoholic fatty liver disease with or without cirrhosis: a population-based study. *BMC Gastroenterol* 21 (1): 394. doi: 10.1186/s12876-021-01978-0.

Piscaglia, F., Svegliati-Baroni, G., Barchetti, A. et al. (2016). Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology* 63 (3): 827–838. doi: 10.1002/hep.28368.

Psyrri, A. and DiMaio, D. (2008). Human papillomavirus in cervical and head-and-neck cancer. *Nat Clin Pract Oncol* 5 (1): 24–31. doi: 10.1038/ncponc0984.

Ratziu, V., Sanyal, A.J., Loomba, R. et al. (2019). REGENERATE: design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis. *Contemp Clin Trials* 84: 105803. doi: 10.1016/j.cct.2019.06.017.

Rauch, A., Kutalik, Z., Descombes, P. et al. (2010). Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 138 (4): 1338–1345, 1345.e1–7. doi: 10.1053/j.gastro.2009.12.056.

Ravaioli, M., Grazi, G.L., Piscaglia, F. et al. (2008). Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant: Off J Am Soc Transplant Am Soc Transplant Surgeons* 8 (12): 2547–2557. doi: 10.1111/j.1600-6143.2008.02409.x.

Regad, T. (2015). Targeting RTK signaling pathways in cancer. *Cancers* 7 (3): 1758–1784. doi: 10.3390/cancers7030860.

Reyes, C.V. (2008). Hepatocellular carcinoma in Wilson disease-related liver cirrhosis. *Gastroenterol hepatol* 4 (6): 435–437. Available at http://www.ncbi.nlm.nih.gov/pubmed/21904521 (accessed on 15th March 2023).

Rice, M.A., Malhotra, S.V., and Stoyanova, T. (2019). Second-generation antiandrogens: from discovery to standard of care in castration resistant prostate cancer. *Front Oncol* 9: 801. doi: 10.3389/fonc.2019.00801.

Roberts, L.R., Sirlin, C.B., Zaiem, F. et al. (2018). Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Hepatology* 67 (1): 401–421. doi: 10.1002/hep.29487.

Robinson, D.R., Wu, Y.-M., and Lin, S.-F. (2000). The protein tyrosine kinase family of the human genome. *Oncogene* 19 (49): 5548–5557. doi: 10.1038/sj.onc.1203957.

Roche, B., Coilly, A., Duclos-Vallee, J.C. et al. (2018). The impact of treatment of hepatitis C with DAAs on the occurrence of HCC. *Liver Int* 38: 139–145. doi: 10.1111/liv.13659.

Rockey, D.C., Caldwell, S.H., Goodman, Z.D. et al. (2009). Liver biopsy. *Hepatology* 49 (3): 1017–1044. doi: 10.1002/hep.22742.

Romeo, S., Kozlitina, J., Xing, C. et al. (2008). Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 40 (12): 1461–1465. doi: 10.1038/ng.257.

Roth, W.K., Weber, M., Buhr, S. et al. (2002). Yield of HCV and HIV-1 NAT after screening of 3.6 million blood donations in central Europe. *Transfusion* 42 (7): 862–868. doi: 10.1046/j.1537-2995.2002.00129.x.

Safi, W., Rauscher, I., and Umgelter, A. (2015). Contrast-induced acute kidney injury in cirrhotic patients. A retrospective analysis. *Ann Hepatol* 14 (6): 895–901. doi: 10.5604/16652681.1171779.

Santillan, C., Chernyak, V., and Sirlin, C. (2018). LI-RADS categories: concepts, definitions, and criteria. *Abdom Radiol (New York)* 43 (1): 101–110. doi: 10.1007/s00261-017-1334-x.

Semelka, R.C., Martin, D.R., Balci, C. et al. (2001). Focal liver lesions: comparison of dual-phase CT and multisequence multiplanar MR imaging including dynamic gadolinium enhancement. *J Magn Reson Imaging* 13 (3): 397–401. doi: 10.1002/jmri.1057.

Shah, S., Shukla, A., and Paunipagar, B. (2014). Radiological features of hepatocellular carcinoma. *J Clin Exp Hepatol* 4 (Suppl 3): S63–6. doi: 10.1016/j.jceh.2014.06.009.

Shen, H., Luan, F., Liu, H. et al. (2008). ZHX2 is a repressor of alpha-fetoprotein expression in human hepatoma cell lines. *J Cell Mol Med* 12 (6B): 2772–2780. doi: 10.1111/j.1582-4934.2008.00233.x.

Shen, X. and Shen, X. (2021). A potential role for aspirin in the prevention and treatment of cholangiocarcinoma. *Int J Cancer* 148 (6): 1323–1330. doi: 10.1002/ijc.33323.

Shin, S., Lee, S.H., Lee, M. et al. (2020). Aspirin and the risk of hepatocellular carcinoma development in patients with alcoholic cirrhosis. *Medicine* 99 (9): e19008. doi: 10.1097/MD.0000000000019008.

Siegel, R.L., Miller, K.D., and Jemal, A. (2018). Cancer statistics, 2018. *CA Cancer J Clin* 68 (1): 7–30. doi: 10.3322/caac.21442.

Silva, M.A., Hegab, B., Hyde, C. et al. (2008). Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut* 57 (11): 1592–1596. doi: 10.1136/gut.2008.149062.

Simon, T.G., Ma, Y., Ludvigsson, J.F. et al. (2018). Association between aspirin use and risk of hepatocellular carcinoma. *JAMA oncol* 4 (12): 1683–1690. doi: 10.1001/jamaoncol.2018.4154.

Simon, T.G., Henson, J., Osganian, S. et al. (2019). Daily aspirin use associated with reduced risk for fibrosis progression in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol : Off Clin Pract J Am Gastroenterol Ass* 17 (13): 2776–2784.e4. doi: 10.1016/j.cgh.2019.04.061.

Simon, T.G., Duberg, A.S., Aleman, S. et al. (2020). Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N Engl J Med* 382 (11): 1018–1028. doi: 10.1056/NEJMoa1912035.

Singal, A.G., Yopp, A.C., Gupta, S. et al. (2012). Failure rates in the hepatocellular carcinoma surveillance process. *Cancer Prev Res (Phila, Pa)* 5 (9): 1124–1130. doi: 10.1158/1940-6207.CAPR-12-0046.

Singal, A.G., Li, X., Tiro, J. et al. (2015). Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. *Am J Med* 128 (1): 90.e1–90.e7. doi: 10.1016/j.amjmed.2014.07.027.

Singal, A.G., Tiro, J., Li, X. et al. (2017). Hepatocellular carcinoma surveillance among patients with cirrhosis in a population-based integrated health care delivery system. *J Clin Gastroenterol* 51 (7): 650–655. doi: 10.1097/MCG.0000000000000708.

Singal, A.G., Lampertico, P., and Nahon, P. (2020). Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J Hepatol* 72 (2): 250–261. doi: 10.1016/j.jhep.2019.08.025.

Singal, A.G., Pillai, A., and Tiro, J. (2014). Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS med* 11 (4): e1001624. doi: 10.1371/journal.pmed.1001624.

Singal, A.K., Salameh, H., Kuo, Y.-F. et al. (2013). Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. *Aliment Pharmacol Ther* 38 (2): 98–106. doi: 10.1111/apt.12344.

Singh, S., Singh, P.P., Singh, A.G. et al. (2013). Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am. J. Gastroenterol* 108 (6): 881–891. quiz 892, doi: 10.1038/ajg.2013.5.

Stevens, C.E., Beasley, R.P., Tsui, J. et al. (1975). Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 292 (15): 771–774. doi: 10.1056/NEJM197504102921503.

Sudhesh Dev, S., Zainal Abidin, S.A., Farghadani, R. et al. (2021). Receptor tyrosine kinases and their signaling pathways as therapeutic targets of curcumin in cancer. *Front Pharmacol* 12: doi: 10.3389/fphar.2021.772510.

Sun, T., Tang, Y., Sun, D. et al. (2018). Osteopontin versus alpha-fetoprotein as a diagnostic marker for hepatocellular carcinoma: a meta-analysis. *Onco Targets Ther* 11: 8925–8935. doi: 10.2147/OTT.S186230.

Sun, X., Mei, J., Lin, W. et al. (2021). Reductions in AFP and PIVKA-II can predict the efficiency of anti-PD-1 immunotherapy in HCC patients. *BMC Cancer* 21 (1): 775. doi: 10.1186/s12885-021-08428-w.

Szpakowski, J.-L., Drasin, T.E., and Lyon, L.L. (2017). Rate of seeding with biopsies and ablations of hepatocellular carcinoma: a retrospective cohort study. *Hepatol Commun* 1 (9): 841–851. doi: 10.1002/hep4.1089.

Takayasu, K., Arii, S., Kudo, M. et al. (2012). Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. *J Hepatol* 56 (4): 886–892. doi: 10.1016/j.jhep.2011.10.021.

Talerman, A., Haije, W.G., and Baggerman, L. (1980). Serum alphafetoprotein (AFP) in patients with germ cell tumors of the gonads and extragonadal sites: correlation between endodermal sinus (yolk sac) tumor and raised serum AFP. *Cancer* 46 (2): 380–385. doi: 10.1002/1097-0142(19800715)46:2<380::aid-cncr2820460228>3.0.co;2-u.

Tang, A., Bashir, M.R., Corwin, M.T. et al. (2018). Evidence Supporting LI-RADS major features for CT- and MR imaging–based diagnosis of hepatocellular carcinoma: a systematic review. *Radiology* 286 (1): 29–48. doi: 10.1148/radiol.2017170554.

Tangkijvanich, P., Anukulkarnkusol, N., Suwangool, P. et al. (2000). Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol* 31 (4): 302–308. doi: 10.1097/00004836-200012000-00007.

Tatarinov, I.S. (1964). Detection of embryo-specific alpha-globulin in the blood serum of a patient with primary liver cancer. *Vopr Med Khim* 10: 90–91. Available at http://www.ncbi.nlm.nih.gov/pubmed/14207501.

Taylor, E.J., Jones, R.L., Guthrie, J.A. et al. (2017). Modeling the benefits and harms of surveillance for hepatocellular carcinoma: information to support informed choices. *Hepatology* 66 (5): 1546–1555. doi: 10.1002/hep.29315.

Tayob, N., Christie, I., Richardson, P. et al. (2019). Validation of the hepatocellular carcinoma early detection screening (hes) algorithm in a cohort of veterans with cirrhosis. *Clin Gastroenterol Hepatol : Off Clin Pract J Am Gastroenterol Ass* 17 (9): 1886–1893.e5. doi: 10.1016/j.cgh.2018.12.005.

Terrault, N.A., Lok, A.S.F., McMahon, B.J. et al. (2018). Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 67 (4): 1560–1599. doi: 10.1002/hep.29800.

Thomas, D.L., Thio, C.L., Martin, M.P. et al. (2009). Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 461 (7265): 798–801. doi: 10.1038/nature08463.

Toso, C., Meeberg, G., Hernandez-Alejandro, R. et al. (2015). Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: a prospective validation. *Hepatology (Baltimore, Md)* 62 (1): 158–165. doi: 10.1002/hep.27787.

Trevisani, F., D'Intino, P.E., Morselli-Labate, A.M. et al. (2001). Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol* 34 (4): 570–575. doi: 10.1016/s0168-8278(00)00053-2.

Trinchet, J.-C., Bourcier, V., Chaffaut, C. et al. (2011). Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. *Hepatology (Baltimore, Md)* 54 (6): 1987–1997. doi: 10.1002/hep.24545.

Trinchet, J.-C., Chaffaut, C., Bourcier, V. et al. (2015). Complications and competing risks of death in compensated viral cirrhosis (ANRS CO12 CirVir prospective cohort). *Hepatology (Baltimore, Md)* 62 (3): 737–750. doi: 10.1002/hep.27743.

Trivedi, P.J., Lammers, W.J., van Buuren, H.R. et al. (2016). Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 65 (2): 321–329. doi: 10.1136/gutjnl-2014-308351.

Tsai, S.L., Huang, G.T., Yang, P.M. et al. (1990). Plasma des-gamma-carboxyprothrombin in the early stage of hepatocellular carcinoma. *Hepatology (Baltimore, Md)* 11 (3): 481–488. doi: 10.1002/hep.1840110321.

Tzartzeva, K., Obi, J., Rich, N.E. et al. (2018). Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology* 154 (6): 1706–1718.e1. doi: 10.1053/j.gastro.2018.01.064.

van der Pol, C.B., Lim, C.S., Sirlin, C.B. et al. (2019). Accuracy of the liver imaging reporting and data system in computed tomography and magnetic resonance image analysis of hepatocellular carcinoma or overall malignancy—A systematic review. *Gastroenterology* 156 (4): 976–986. doi: 10.1053/j.gastro.2018.11.020.

Vaz, N.F., Margon, J.F., Moutinho, B.D. et al. (2020). 'Hepatocellular carcinoma in patients with autoimmune hepatitis: prevalence and risk factors'. *J Hepatol* 73: S465. doi: 10.1016/S0168-8278(20)31412-4.

Venkatesh, S.K., Chandan, V., and Roberts, L.R. (2014). Liver masses: a clinical, radiologic, and pathologic perspective. *Clin Gastroenterol Hepatol* 12 (9): 1414–1429. doi: 10.1016/j.cgh.2013.09.017.

Ventura-Cots, M., Ballester-Ferré, M.P., Ravi, S. et al. (2019). 'Public health policies and alcohol-related liver disease.'. *JHEP Rep : Innovation Hepatol* 1 (5): 403–413. doi: 10.1016/j.jhepr.2019.07.009.

Vilana, R., Forner, A., Bianchi, L. et al. (2010). Intrahepatic peripheral cholangiocarcinoma in cirrhosis patients may display a vascular pattern similar to hepatocellular carcinoma on contrast-enhanced ultrasound. *Hepatology* 51 (6): 2020–2029. doi: 10.1002/hep.23600.

Vogelstein, B., Papadopoulos, N., Velculescu, V.E. et al. (2013). Cancer genome landscapes. *Science (New York, N Y)* 339 (6127): 1546–1558. doi: 10.1126/science.1235122.

Vongsuvanh, R., van der Poorten, D., Iseli, T. et al. (2016). Midkine increases diagnostic yield in afp negative and nash-related hepatocellular carcinoma. *PloS one* 11 (5): e0155800. doi: 10.1371/journal.pone.0155800.

Wait, S., Kell, E., Hamid, S. et al. (2016). Hepatitis B and hepatitis C in southeast and southern Asia: challenges for governments. *Lancet Gastroenterol Hepatol* 1 (3): 248–255. doi: 10.1016/S2468-1253(16)30031-0.

Wang, B., Huang, G., Wang, D. et al. (2010). Null genotypes of GSTM1 and GSTT1 contribute to hepatocellular carcinoma risk: evidence from an updated meta-analysis. *J Hepatol* 53 (3): 508–518. doi: 10.1016/j.jhep.2010.03.026.

Wang, B.-Q., Wang, Y.-L., and Shi, K.-Q. (2017). Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. *Liver Int : Off J Int Ass Study Liver* 37 (2): 309–310. doi: 10.1111/liv.13289.

West, J., Card, T.R., Aithal, G.P. et al. (2017). Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: a population-based cohort study. *Aliment Pharmacol Ther* 45 (7): 983–990. doi: 10.1111/apt.13961.

Wilson, F.R., Coombes, M.E., Wylie, Q. et al. (2017). Herceptin® (trastuzumab) in HER2-positive early breast cancer: protocol for a systematic review and cumulative network meta-analysis. *Syst Rev* 6 (1): 196. doi: 10.1186/s13643-017-0588-2.

Wong, R.J., Cheung, R., and Ahmed, A. (2014). Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology (Baltimore, Md)* 59 (6): 2188–2195. doi: 10.1002/hep.26986.

World Health Organization (WHO) (2016). Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. *World Health Organization*.

Wu, M., Li, L., Wang, J. et al. (2018). Contrast-enhanced US for characterization of focal liver lesions: a comprehensive meta-analysis. *Eur Radiol* 28 (5): 2077–2088. doi: 10.1007/s00330-017-5152-x.

Yamamoto, K., Imamura, H., Matsuyama, Y. et al. (2010). AFP, AFP-L3, DCP, and GP73 as markers for monitoring treatment response and recurrence and as surrogate markers of clinicopathological variables of HCC. *J Gastroenterol* 45 (12): 1272–1282. doi: 10.1007/s00535-010-0278-5.

Yang, J.D., Addissie, B.D., Mara, K.C. et al. (2019). GALAD score for hepatocellular carcinoma detection in comparison with liver ultrasound and proposal of GALADUS score. *Cancer Epidemiol Biomarkers Prev : A Publication Am Ass Cancer Res, Cosponsored Am Soc Prev Oncol* 28 (3): 531–538. doi: 10.1158/1055-9965.EPI-18-0281.

Yang, Z.F. and Poon, R.T.P. (2008). Vascular changes in hepatocellular carcinoma. *Anat Rec: Adv Integrative Anatomy Evolutionary Biol* 291 (6): 721–734. doi: 10.1002/ar.20668.

Younossi, Z.M., Koenig, A.B., Abdelatif, D. et al. (2016). Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 64 (1): 73–84. doi: 10.1002/hep.28431.

Yuen, M.-F., Chen, D.-S., Dusheiko, G.M. et al. (2018). Hepatitis B virus infection. *Nat Rev Dis Primers* 4: 18035. doi: 10.1038/nrdp.2018.35.

Zhai, M., Long, J., Liu, S. et al. (2021). The burden of liver cirrhosis and underlying etiologies: results from the global burden of disease study 2017. *Aging* 13 (1): 279–300. doi: 10.18632/aging.104127.

Zhang, B.-H., Yang, B.-H., and Tang, Z.-Y. (2004). Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 130 (7): doi: 10.1007/s00432-004-0552-0.

Zhang, H.-L., Yu, L.-X., Yang, W. et al. (2012). Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. *J Hepatol* 57 (4): 803–812. doi: 10.1016/j.jhep.2012.06.011.

Zhang, Y., Li, T., Qiu, Y. et al. (2017). Serum microRNA panel for early diagnosis of the onset of hepatocellular carcinoma. *Medicine* 96 (2): e5642. doi: 10.1097/MD.0000000000005642.

Zheng, S.-S., Xu, X., Wu, J. et al. (2008). Liver transplantation for hepatocellular carcinoma: hangzhou experiences. *Transplantation* 85 (12): 1726–1732. doi: 10.1097/TP.0b013e31816b67e4.

Zhu, A.X., Duda, D.G., Sahani, D.V. et al. (2011). HCC and angiogenesis: possible targets and future directions. *Nat Rev Clin Oncol* 8 (5): 292–301. doi: 10.1038/nrclinonc.2011.30.

Zhu, A.X., Kang, Y.-K., Yen, C.-J. et al. (2015). Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 16 (7): 859–870. doi: 10.1016/S1470-2045(15)00050-9.

Zhu, A.X., Park, J.O., Ryoo, B.-Y. et al. (2019). Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 20 (2): 282–296. doi: 10.1016/S1470-2045(18)30937-9.

17 Pancreatic and Biliary Tract Cancers

Risk Factors and Etiology, Screening, Surveillance, and Biomarkers of Detection and Prognosis

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Pancreatic Cancer

Introduction

Globally, annual new cases of pancreatic cancer (PC) are estimated at half a million, a figure which is largely paralleled by the number of associated deaths (~ 466,000) (Sung et al. 2021). The low five-year survival rates (3–15%) are explained by a most often late-stage diagnosis (Pereira et al. 2020; Sung et al. 2021). Ductal adenocarcinoma of the pancreas (PDAC) is the seventh leading cause of cancer associated mortality, and due to a rise in obesity, diabetes mellitus incidence and alcohol consumption in developed countries (Europe, North America, and Oceania), it is projected to surpass other common cancers (such as colon, breast) by 2030 (Kamisawa et al. 2016; Sung et al. 2021). Early tumor detection is key in PC, as extended survival can be achieved when lesions are detected at a pre-invasive stage or when tumors are smaller than 2 cm and are still localized (Marchegiani et al. 2017). Resectable tumors, however, are identified in less than 20% of cases – a dismal figure which could potentially be improved by early PC detection (Pereira et al. 2020; Zerboni et al. 2019).

A relatively low incidence (~10 in 100,000) and 1.3% lifetime risk for PDAC preclude asymptomatic, average-risk adult (>50 age) screening; however ~85% of PC patients present at a late and non-operable stage following a relatively vague clinical course which challenges early recognition. While most cases present with significant weight loss, painless jaundice, and occasionally proximal gastrointestinal obstruction (positive predictive value (PPV) of 4–13%), these are usually late signs, with jaundice suggesting biliary obstruction by pancreatic head and neck tumors (~70% of cases) (Hidalgo 2010; Schmidt-Hansen et al. 2016).

Early, non-specific symptoms such as epigastric or back pain, indigestion, nausea and abdominal bloating, change in bowel habit, pale stools, depression and fatigue are weak predictors (PPV<0.5%), and due to their intermittent nature often result in recurrent primary care consultations and delays in diagnosis (Schmidt-Hansen et al. 2016; Stapley et al. 2012).

Furthermore, the relatively low specificities of single test diagnostics result in unacceptable rates of false positives, which can lead to further unnecessary investigatory procedures or interventions including Endoscopic Retrograde Cholangiopancreatography or extensive pancreatic resections which are associated with high morbidity (up to 64%) or mortality (2–5%) (Owens et al. 2019). Screening for PC in high-risk individuals (>5% risk) however, can reduce false positive test results, improve resectable PC detection with reduced perioperative morbidity and mortality. In individuals with high-risk pancreatic cysts and genetic predisposition or familial clustering of PC cases, screening is internationally recommended using annual cross-sectional imaging and blood tumor marker levels. Surveillance is generally recommended from age 50 years, with earlier (as early as 35) onset of screening on the background of known highly penetrant genetic mutations (STK11 and PRSS1) (Aslanian et al. 2020; European evidence-based guidelines on pancreatic cystic neoplasms 2018). As many as 0.8% of high-risk individuals (HRI) develop new onset diabetes up to three-years prior to PC diagnosis, and monitoring for rising blood glucose levels in HRI as further means of risk stratification is also recommended (Goggins et al. 2020).

Risk Factors

Risk factors for PDAC are generally categorized into modifiable and non-modifiable (Table 1). Here, we explore the evidence for pancreatic cancer-associated risk factors and consider

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the data supporting risk reduction strategies. We also explore the role of chemo-preventative agents, and comment on current strategies under development to aid early detection in high-risk groups.

Modifiable

Smoking

The risk of pancreatic cancer is significantly higher in current (RR: 1.8; 95% CI, 1.7–1.9) and former (RR: 1.2; 95% CI, 1.1–1.2) smokers than in non-smokers (Lugo et al. 2018). There is a "dose-dependent" relationship with risk positively correlated with the number of cigarettes smoked. Similarly, risk reduces with smoking cessation. Interplay has been demonstrated between smoking, family history of pancreatic cancer, and diabetes status, with a higher cancer risk amongst current smokers with a family history of the disease (aOR: 2.24; 95% CI, 0.66–7.6) and former smokers with diabetes mellitus (aOR: 1.44; 95% CI, 0.91–2.28) (Molina-Montes et al. 2020).

Alcohol

High alcohol intake increases the risk of PDAC, with the risk increased by 15% (RR: 1.15; 95% CI, 1.06–1.25) in heavy drinkers (average alcohol consumption ≥ 24 grams alcohol/day; where one alcoholic beverage is defined as containing 12 grams alcohol) (Wang et al. 2016). Wang et al. show the risk of PDAC associated with alcohol intake to be J-shaped, with only those drinking large amounts having a marked increased risk. As with smoking risk, alcohol intake exhibits an interaction with other risk factors. Individuals with impaired fasting glucose (IFG) who drink more than 30 g/day were observed to have a 38% increased pancreatic cancer risk (HR, 1.38; 95% CI, 1.23–1.54). Notably, for all individuals with IFG, risk of PDAC increased linearly with alcohol intake, suggesting that complete alcohol abstinence for those with impaired glucose tolerance and diabetes mellitus, may reduce pancreatic cancer risk (Park et al. 2022).

Chronic Pancreatitis

In chronic pancreatitis, parenchymal injury, progressive inflammation and fibrosis occur due to intra-pancreatic activation of digestive enzymes. In around 70% of chronic pancreatitis cases, alcohol abuse is the underlying cause while other main etiologies are hereditary (PRSS1/SPINK1 mutations) and idiopathic (Midha et al. 2016, Rawla et al. 2019). The chronic inflammation is related to development of KRAS mutations, pancreatic intraepithelial neoplasms (PanINs), acinar-to-ductal metaplasia and progression to PDAC (Greenhalf et al. 2020). The development of PDAC on the background of chronic pancreatitis occurs over decades with a 20-year cumulative risk of around 5% (Midha et al. 2016). In patients with hereditary pancreatitis (PRSS1 mutations) a younger age at PDAC diagnosis is a feature and the reported lifetime risk for PC could be as high as 40% (Bartsch et al. 2012). The higher risk in these cohorts highlights the importance of registries such as the EUROPAC study (European Registry of Hereditary Pancreatitis and Familial Pancreas Cancer; Liverpool University, UK) in screening and surveillance of hereditary pancreatitis families (Greenhalf et al. 2020). Although screening for PDAC in patients with chronic pancreatitis is not established practice, experts advise maintaining a high index of suspicion in cases with high-risk clinical findings (e.g., abdominal pain, new onset diabetes, jaundice, and significant weight loss) (Sheth et al. 2017).

Obesity

The relationship between obesity and carcinogenesis is complex. Obesity (Body Mass Index ≥30kg/m^2) increases the risk of pancreatic cancer (HR = 1.81; 1.11–2.95) (Christakoudi et al. 2021). The mechanisms for increased oncogenicity may be related to inflammation, changes in microbiota, hormones, adipokines, and dietary factors (Cascetta et al. 2018). There is evidence that bariatric surgery, which is currently the most effective treatment for obesity, can reduce the risk of pancreatic cancer (HR 0.46, 95% CI 0.22, 0.97, P = 0.04), although the variability in risk reduction profiles between different types of bariatric surgery procedures is not well understood (Schauer et al. 2019). It is likely that the different procedures influence systemic inflammation and alter adipokine profiles differently. Understanding the mechanisms underpinning differences in pathophysiological changes in bariatric surgery will be important to both clarify the relationship between obesity and PDAC and to understand how medical and surgical weight-loss treatments can be used to reduce the risk of PDAC in the future.

Diet

PADC risk has been linked to high fructose (RR Z 1.22; 95% CI: 1.08 – 1.37), and red and processed meat intake (Aune et al. 2012), although the evidence for this is variable. Dietary effects are likely to be multifactorial and either increase obesity-related oncogenesis, or relate to changes in microbiome. A recent study investigated whether a diabetes risk reduction diet altered the chances of developing PDAC. Irrespective of whether individuals had a diagnosis of diabetes, adherence to the diet measured using the Diabetes Risk Reduction Diet (DRRD) score was inversely related to PDAC risk (ORs of 0.55 (95% confidence interval, CI 0.38–0.80) for the highest versus the lowest score tertile (p for trend across tertiles = 0.002)). Factors taken into account with this score included intake of fiber load, fruit, coffee, saturated fat, dietary glycemic index, red/processed meat and fructose drinks (Turati et al. 2022).

Environmental Risk

A number of petrochemicals have been related to increased pancreatic cancer risk including pesticides (Ji et al. 2001), aromatic hydrocarbons (Antwi et al. 2015), and heavy metals (Amaral et al. 2012). Recently the baseline plasma levels of twenty-two persistent organic pollutants (POPs) were compared between 513 pancreatic cancer cases and 1,020 matched controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (Porta et al. 2022). Increasing concentrations of some POPs conferred slight increased risks of PDAC. However, the majority of the 22 POPs, when assessed individually or in combination either conferred no increased risk or only a moderately increased of PDAC (Porta et al. 2022).

Non-Modifiable

Age

PDAC occurs more frequently in the elderly. In the USA, the median age of diagnosis is 70 years, with only 10.6% of patients diagnosed before the age of 55 years (Cai et al. 2021). It has been suggested that increased cancer risk with age may be attributable to telomere dysfunction as a molecular mechanism of carcinogenesis (Matsuda 2019). Interestingly, a recent study by Yuan et al. investigated the age-dependent association of modifiable risk factors with pancreatic cancer among 167,483 participants from across the US and Europe (Yuan et al. 2022). The authors suggest that for established risk factors such as cigarette smoking, obesity, and diabetes, stronger associations and greater attributable risk for PDAC were found amongst younger individuals (age <70 years). This is important for public health measures that aim to support risk reduction which will require implementation at younger ages.

Prevention

The use of chemo preventive drugs to inhibit or delay the development of PDAC has been investigated along with their mechanistic effects for possible future therapies. The results of these studies have been variable. A study observing the risk among participants from prospective cohort studies found no association between aspirin and future risk of pancreatic cancer (Khalaf et al. 2018), whereas another study showed that long term aspirin use led to a reduction in pancreas cancer compared to those who had not been prescribed aspirin (Tsoi et al. 2019). Additionally, the use of metformin along with aspirin has been reported to show a more significant reduction in cancer risk compared to when using aspirin or metformin alone (Sung et al. 2020). Statins have also been associated with reduced risk of PDAC in patients with type 2 diabetes (T2DM), with a study showing a significant dose-response effect (Chen et al. 2016).

With respect to chronic pancreatitis, surgical reduction of inflammatory tissue in the form of total pancreatectomy with islet auto-transplantation (TPIAT) has been proposed with the purpose of PC risk reduction (e.g., in hereditary pancreatitis) and prevention of Type 3c diabetes (Bellin et al. 2018, 2014). However, due to lack of sufficient evidence, incomplete protection against diabetes and high peri-operative morbidity (including metabolic derangements and lifelong enzyme replacement therapy), TPIAT is mostly recommended for management of intractable pain. Cases with higher risk for developing PC should be individually considered in conjunction with patient wishes (Bellin et al. 2014).

High Risk Groups, Screening, and Surveillance

Over the past decade, international healthcare organizations debated over the target population (high risk groups), the appropriate modalities by which screening should be performed and the frequency of follow up. Expert opinions have been consolidated into specific recommendations by the American College of Gastroenterology (ACG 2015), the American Society of Clinical Oncology (ASCO 2019), the American Gastroenterological Association (AGA 2020), and the International Cancer of the Pancreas Screening Consortium (CAPS 2019), for patients with genetic susceptibility for PC. Meta-analyses of international cohort studies supported a consensus that identifying known PDAC precursor lesions prior to parenchymal invasion in HRI is ideal considering the higher prevalence (pooled) in this cohort (up to 3.3%) compared to an average-risk population, and that their timely surgical resection extends patient overall survival (Corral et al. 2019; Signoretti et al. 2018). As recommended by CAPS, PanINs, intraductal papillary mucinous neoplasms (IPMNs), and T1N0M0 PDACs should be targeted for early detection (Goggins et al. 2020). The detection of such generally small lesions, however, requires the use of adequately sensitive imaging modalities, and MRI (and MR-cholangiopancreatography; MRCP) complemented by endoscopic ultrasonography (EUS) have been established as ideal tools. While better visualization of cystic lesions is possible with MRI, for solid pancreatic lesions (< 2cm) EUS shows higher sensitivity and enables sampling by fine needle aspiration or biopsy for further cytological or histological characterization of both cystic and solid lesions (Zerboni et al. 2019).

Familial Pancreatic Cancer and Inherited Risk

Age, a positive family history of PC, and/or the presence of certain germline mutations guide risk stratification and determine patient eligibility for surveillance (Goggins et al. 2020). Although PC is mostly sporadic (90%) with a median age at diagnosis of 71 years (ranging 60–80), 5–10% of cases are estimated as familial, and up to 5% develop in patient with specific cancer associated genetic syndromes (e.g., BRCA1/2 hereditary breast ovarian cancer, Lynch, Peutz-Jeghers, and Li-Fraumeni syndromes) in which earlier onset due to genetic anticipation (<50) is observed (Goggins et al. 2020; Kamisawa et al. 2016; McFaul 2006).

Multiple germline mutations have been linked with PDAC (Lowenfels and Maisonneuve 2006), and PC susceptibility genes which are associated with specific hereditary cancer syndromes include ***BRCA1*, *BRCA2*,** and ***PALB2*** (hereditary breast and ovarian cancer; HBOC), ***CDKN2A*** (familial atypical multiple mole melanoma; FAMMM), ***ATM*** (ataxia-telangiectasia), ***APC*** (familial adenomatous polyposis), ***MLH1/MLH2/MSH2*** and ***MSH6*** (Lynch syndrome), ***PRSS1*** (hereditary pancreatitis), and ***STK11/LKB1*** (Peutz-Jeghers syndrome). Recommendations for surveillance, however, vary depending on the overall risk for PC associated with each PC susceptibility gene (Aslanian et al. 2020; Goggins et al. 2020; Lowenfels and Maisonneuve 2006; Maisonneuve and Lowenfels 2015). Protocol variations are explained by the fact that altogether less than 20% of familial PC (FPC) cases are attributed to germline mutations in these genes, and even in their presence these mostly manifest as other forms of cancer than pancreatic (E.g. breast and ovarian in HBOC or multiple melanoma in FAMMM, colonic cancer in Lynch syndrome). Moreover, positive family history of PC without apparent mutations in these genes, as well as the presence of similar mutations in sporadic cases, suggest that surveillance of genetically susceptible individuals should be context specific (Pereira et al. 2020).

Where family history of PC is absent, the existence of hereditary cancer syndromes on their own are not an indication for PC surveillance, apart from two exceptions. One such is Peutz-Jeghers syndrome (*STK11* mutation carriers), where 132-fold risk and up to a 36% lifetime risk for PC by age 70 are reported. PRSS1 mutations (hereditary pancreatitis) with long standing chronic (calcific) pancreatitis is another exception, in which a 40% lifetime risk for PC exists (Bartsch et al. 2012). Due to a younger age (mean) of PDAC development in these patients (40 years for Peutz-Jeghers syndrome and 54 years for hereditary pancreatitis) early initiation of surveillance is recommended – as early as 35 and 40 for Peutz-Jeghers syndrome and hereditary pancreatitis, respectively (Aslanian et al. 2020; Goggins et al. 2020).

Although pathogenic germline mutations in *BRCA2* (RR 3.5–6.2, 95% CI 1.87–6.58), CDKN2A (RR 13–39), TP53 (Li-Fraumeni syndrome; RR 7.3, 95% CI 2–19), MLH1/MSH2/MSH6 (Lynch syndrome; RR 8.6–11), ATM (RR 3.92, 95% CI 0.44–14.2), carry risk for PC, due to low (or incomplete) penetrance of these genes surveillance is only recommended in the presence of a PC-affected first degree relative (FDR) (or at least two non-FDRs). Apart from genetic susceptibility, factors such as common habits (alcohol consumption and smoking) or shared environmental exposures can explain familial clustering of cancers. In the context of PDAC, an example of the latter are common *H. Pylori* infections within families, which is a known risk factor for PC (Turati et al. 2013).

In the absence of a known genetic cancer syndrome, the presence of two or more cases of PC among FDRs are defined as familial pancreatic cancer (FPC), and in such cases, screening is recommended by an international consortium of experts (CAPS – International Cancer of the pancreas screening (CAPS) consortium) (Goggins et al. 2020). Compared to a 1.3% lifetime risk in the general population, in individuals with one FDR with PC the lifetime risk roughly doubles. In patients with two first-degree relatives diagnosed with PC the estimated risk rises to ~8%, and a 40% (32-fold) risk was observed in those with three or more affected FDRs in prospective population studies (Canto et al. 2013). Surveillance in such subjects should start at either the age of 50, or 10 years younger than the age at which the youngest FDR was diagnosed (Aslanian et al. 2020; Goggins et al. 2020). Furthermore, genetic counselling and testing is advised where family history of PC exists in Jewish (Ashkenazi) individuals, and specifically for the 6174delT variant observed in 1% of this population (Ferrone et al. 2009).

Considering the markedly higher risk and genetic anticipation in these cohort, established national FPC registries offer screening, surveillance and advance research in the context of early PC detection. The largest three include the first established (1994) registry: the American National Familial Pancreas Tumor Registry (NFPTR, John Hopkins University, Baltimore, US), The EUROPAC trial and the German National Case Collection for Familial Pancreatic Carcinoma (FaPaCa; Phillips University, Marburg, Germany). FPC registries in Italy, Spain, Australia, and Japan have been initiated (Pereira et al. 2020).

Cystic Lesions

The reported prevalence of asymptomatic cystic pancreatic lesions (CLPs) in the healthy adult population ranges between 3 to 49%. CLPs are commonly incidental on abdominal scans (3% on computed tomography, 2.4–49% on MR imaging) performed for other indications than pancreatic, with an age correlated prevalence (van Huijgevoort et al. 2019). An increased prevalence of >1 cm cysts (~50%) is observed in high-risk individuals and can be explained the high-resolution imaging (MRI) used for screening (Goggins et al. 2020; Zerboni et al. 2019). While less than 1% of cysts are detected at a >2cm size, their variable malignant potential warrants differentiation of benign (serous cystic neoplasms; SCNs) from potentially premalignant lesions that are more likely to evolve into invasive cancer (Tanaka et al. 2017). Surgical intervention for SCNs is only indicated in the presence of symptoms associated with mass compression, while asymptomatic SCNs do not require surveillance due to the absence of malignancy risk (Buerlein and Shami 2021; van Huijgevoort et al. 2019).

Alongside PanINs, mucinous cystic lesions (MCL) are also considered non-invasive precursors of PC, as opposed to their low-risk serous counterparts (Vincent et al. 2011). MCLs (intraductal papillary mucinous neoplasms and mucinous cystic neoplasms – IPMNs and MCNs, respectively) give rise to approximately 15% of PC cases (Singhi et al. 2019). Data emerging from studies in surgical cohorts with resected MCLs are suggestive of a 1–8% risk for invasive cancer for IPMNs, and 10–39% for MCNs (van Huijgevoort et al. 2019). For IPMNs, the risk for PC varies based on their extension into the pancreatic ductal system, with high grade dysplasia or invasive cancer found in up to 62% of resections for main duct (MD) and up to 30% in side-branch (SB) IPMNs. Mixed type (MT) IPMNs have a comparable risk to MD-IPMNs, although this is reduced with microscopic involvement of the main duct (van Huijgevoort et al. 2019).

Detectable by imaging, MCLs can be targeted for early PC detection and surgically resected or kept under surveillance, depending on the presence of worrisome clinicopathological features (i.e. degree of dysplasia; size, number of cysts, presence of a solid mass or >5 mm mural nodules, >5 mm main duct dilatation, obstructive jaundice, associated pancreatitis, >5 mm/2-year cyst growth and lymphadenopathy) (fully discussed in Chapter 22). The risk of malignancy, existing comorbidities and overall life expectancy should, however, be first considered. If potential surgical interventions are appropriate, EUS-FNA is performed for further cyst evaluation (Elta et al., 2018; European evidence-based guidelines on pancreatic cystic neoplasms 2018; Megibow et al. 2017; Tanaka et al. 2017).

The increasing number of incidental cysts supports implementation of surveillance programs, and specific recommendations by American (American Gastroenterological Association – AGA, the American College of Gastroenterology – ACG, and the American College of Radiology – ACR), European (European Study Group on Cystic Tumors of the Pancreas) and international (International Association of Pancreatology) associations are published (European evidence-based guidelines on pancreatic cystic neoplasms 2018; Elta et al. 2018; Megibow et al. 2017; Vege et al. 2015; Tanaka et al. 2017).

Excluding MD-IMPNs (which should be surgically resected) or when worrisome features (discussed above) are absent, the surveillance of IPMNs is only indicated in the surgically fit with interval MR-cholangiopancreatography (MRCP), or EUS when MR imaging is contraindicated or not tolerated by the patient. MR imaging is advantageous over CT by eliminating radiation exposure, as well as offers high resolution images of pancreatic parenchymal and cystic structures (e.g. septations, mural nodules). The IAP, ACG, and ACR guidelines advise surveillance intervals based on cyst size as opposed to AGA guidance, which applies a similar screening protocol regardless of the size of the lesion (Figure 1). Furthermore, with respect to the degree of main duct dilatation, variation between guidelines exist; AGA guidance defines a >5 mm dilatation as high risk as opposed to IAP, ACR, and European guidelines, which set the cut-off at >10 mm (European evidence-based guidelines on pancreatic cystic neoplasms 2018; Elta et al. 2018; Megibow et al. 2017; Vege et al. 2015; Tanaka et al. 2017). The recently launched PACYFIC study (international, prospective evaluation of surveillance strategies in 5,000 patients with CLPs; www.PACYFIC.net) aims to close the gaps in evidence and support a consensus for surveillance programs and results are expected in 2024.

Regarding MCNs, surgical resection is recommended according to IAP, European, and AGA guidance. Considering their lower risk for progression at smaller sizes (<40 mm) and in the absence of worrisome features, however, the European guidelines suggest a less aggressive approach where similar surveillance protocol to SB-IPMNs are advised (European evidence-based guidelines on pancreatic cystic neoplasms 2018; Griffin et al. 2017; Postlewait et al. 2017). Following their surgical resection, high risk IPMNs or lesions with main duct involvement or high-grade dysplasia are followed up at six-monthly intervals (for the first two years then annually according to European and biannually if positive family history or non-intestinal cyst histology are present according to IAP guidance), while 6–12 monthly scans are advised for low risk IPMNs post-operatively. Resections of MCNs absent of invasive features are considered curative and do not require further monitoring (van Huijgevoort et al. 2019).

Lifelong surveillance (in the surgically fit) is advised by ACG, the European study group, and the IAP, but not the AGA or ACR. The AGA recommends cessation of surveillance for stable cysts with no progression after a five-year surveillance period, while discharge is advised by ACR either after 10 years of stability or upon patients reaching 80 years of age (Elta et al. 2018; European evidence-based guidelines on pancreatic cystic neoplasms 2018; Tanaka et al. 2017).

New-Onset Diabetes (NOD)

People with new onset diabetes comprise a high-risk group for pancreatic cancer. While individuals who have had T2DM for over five years have a 1 to 1.5-fold increased risk of pancreatic ductal adenocarcinoma (PDAC), the relative risk of PDAC is 6–8 fold in people over 50 years with diabetes mellitus (DM) of less than one year duration (Ben et al. 2011). Approximately 80% of PDAC patients have either DM, advanced pre-diabetes or impaired fasting blood glucose at the time of PDAC diagnosis (Pannala et al. 2008; Permert et al. 1993). Hyperglycemia, first evident 36 to 30 months before PDAC diagnosis, increases steadily, with diabetes observed 12 to 6 months before cancer diagnosis (Sharma et al. 2018). Thus, the onset of DM may be considered a paraneoplastic "symptom" of PDAC and individuals with new-onset DM (NOD) the highest risk group for PDAC. However, for this high-risk group, there are no established guidelines for surveillance are no screening programs exist. Challenges include the lack of validated methods to detect PDAC with the requisite specificity, given the low prevalence of PDAC (approximately 1%) in this high-risk group (Chari et al. 2005). However, work to understand how this high-risk group may be screened in future is proceeding (Chari et al. 2022; Maitra et al. 2018). In the United States, the Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) Consortium is currently amassing a NOD cohort (target 10,000 individuals over 50 years of age), with both clinical data and bio specimens being collected. The study has many aims, including

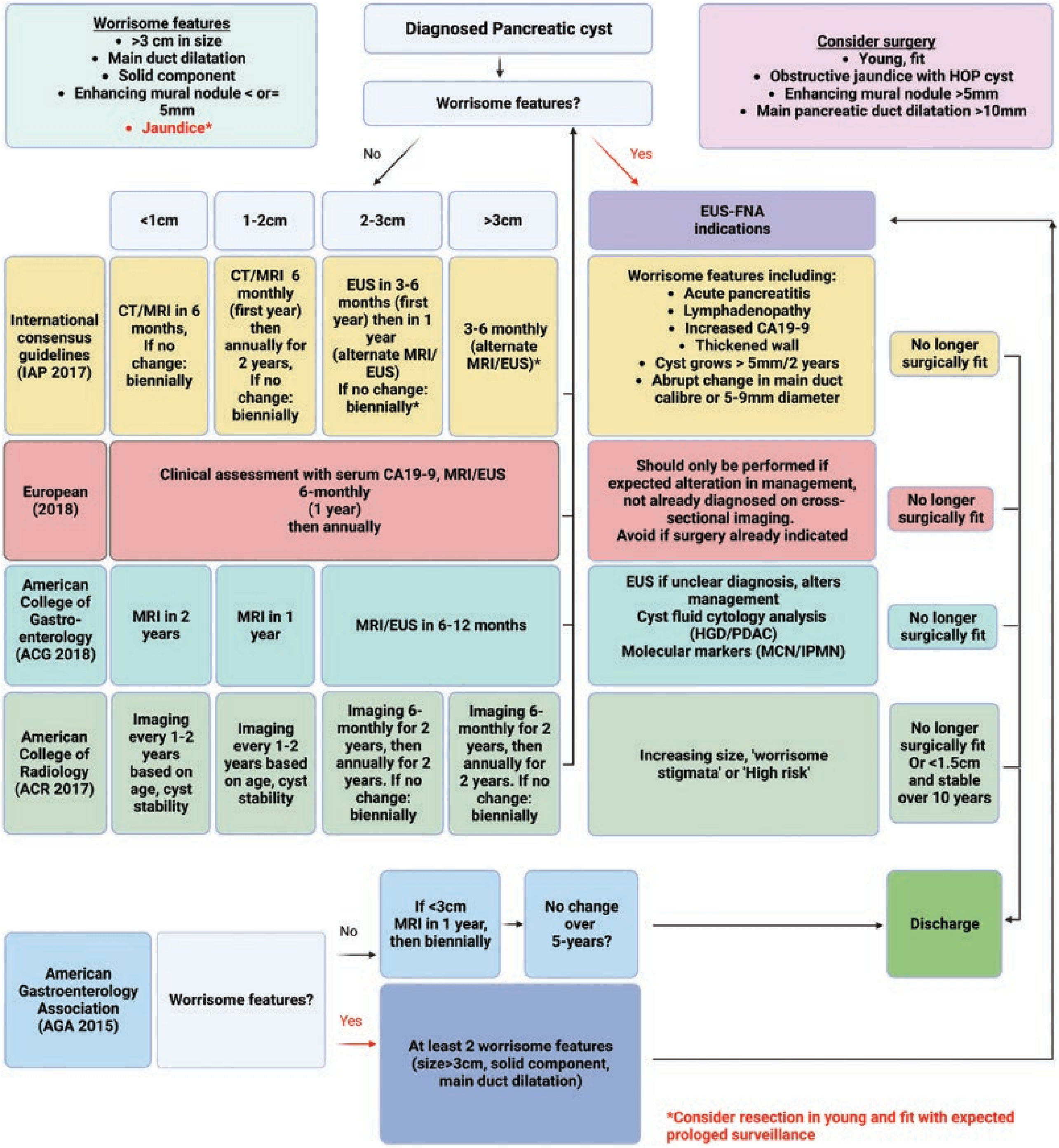
Worrisome features
• >3 cm in size
• Main duct dilatation
• Solid component
• Enhancing mural nodule < or= 5mm
• Jaundice*
Diagnosed Pancreatic cyst
Worrisome features?
Consider surgery
• Young, fit
• Obstructive jaundice with HOP cyst
• Enhancing mural nodule >5mm
• Main pancreatic duct dilatation >10mm
No
Yes
<1cm
1-2cm
2-3cm
>3cm
EUS-FNA indications
International consensus guidelines (IAP 2017)
CT/MRI in 6 months, If no change: biennially
CT/MRI 6 monthly (first year) then annually for 2 years, If no change: biennially
EUS in 3-6 months (first year) then in 1 year (alternate MRI/ EUS) If no change: biennially*
3-6 monthly (alternate MRI/EUS)*
Worrisome features including:
• Acute pancreatitis
• Lymphadenopathy
• Increased CA19-9
• Thickened wall
• Cyst grows > 5mm/2 years
• Abrupt change in main duct calibre or 5-9mm diameter
No longer surgically fit
European (2018)
Clinical assessment with serum CA19-9, MRI/EUS 6-monthly (1 year) then annually
Should only be performed if expected alteration in management, not already diagnosed on cross-sectional imaging. Avoid if surgery already indicated
No longer surgically fit
American College of Gastro-enterology (ACG 2018)
MRI in 2 years
MRI in 1 year
MRI/EUS in 6-12 months
EUS if unclear diagnosis, alters management
Cyst fluid cytology analysis (HGD/PDAC)
Molecular markers (MCN/IPMN)
No longer surgically fit
American College of Radiology (ACR 2017)
Imaging every 1-2 years based on age, cyst stability
Imaging every 1-2 years based on age, cyst stability
Imaging 6-monthly for 2 years, then annually for 2 years. If no change: biennially
Imaging 6-monthly for 2 years, then annually for 2 years. If no change: biennially
Increasing size, 'worrisome stigmata' or 'High risk'
No longer surgically fit Or <1.5cm and stable over 10 years
American Gastroenterology Association (AGA 2015)
Worrisome features?
No
If <3cm MRI in 1 year, then biennially
No change over 5-years?
Discharge
Yes
At least 2 worrisome features (size>3cm, solid component, main duct dilatation)
*Consider resection in young and fit with expected prologed surveillance

Figure 1 Summary of international guidelines for pancreatic cysts surveillance and indication for EUS-FNA. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; EUS-FNA: Endoscopic Ultrasound with Fine Needle Aspiration; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; HGD: High Grade Dysplasia (European evidence-based guidelines on pancreatic cystic neoplasms 2018; Elta et al. 2018; Megibow et al. 2017; Tanaka et al. 2017; Vege et al. 2015).

estimating the probability of PDAC in individuals with NOD, undertaking validation studies of candidate biomarkers to detect PDAC in the NOD group and providing a platform facilitating screening protocols PDAC in individuals with NOD (Maitra et al. 2018). One such study, Early Detection Initiative (EDI) is a randomized controlled trial designed to improve detection of operable PDAC (Chari et al. 2022). The study uses the Enriching New-onset Diabetes for Pancreatic Cancer (ENDPAC) algorithm (Sharma et al. 2018), which stratifies subjects with NOD on the basis of age, and changes in both weight and diabetes parameters. Individuals with high ENDPAC scores are stratified to an intervention arm, which includes imaging. Comparisons will be made of the proportion of late stage PDAC in the intervention and observation study arms.

A Cancer Research UK-funded study, UK Early Detection Initiative (UK-EDI) is currently open in the UK and recruiting people over 50 years of age who are within six months of their diagnosis of diabetes in the UK (Pereira et al. 2020). With recruitment occurring from primary care, specialist diabetes centers and secondary care, this study aims to create a unique resource in the UK, including clinical data blood samples that will be used to inform how best to screen for PDAC in NOD subjects in the UK, including generation of data on the cost-effectiveness of diagnosing PDAC earlier in the setting of NOD. It is envisaged that the UK-EDI resource will support the validation of candidate early PDAC detection biomarkers as well as new biomarker discovery.

Biomarkers

Biomarkers for Detection

A number of approaches to develop biomarkers that could facilitate screening for pancreatic cancer are being investigated. Multi-cancer liquid biopsy tests, such as CancerSEEK and GalleriTM have been tested for their sensitivity and specificity for PDAC. CancerSEEK tests for mutations in cell free DNA and eight cancer-associated blood protein biomarkers and was observed to discriminate diagnosed PDAC from healthy control with a sensitivity and specificity of >70% and >99%, respectively (Cohen et al. 2018). The GalleriTM test, developed by GRAIL, uses methylation signals from targeted circulating free DNA and machine learning classifiers for cancer detection. In a case-controlled observational study, involving subjects already diagnosed with cancer or under investigation for highly suspected cancer, the test detected 61.9% (13/21) of stage I, 60% (12/20) of stage II, 85.7% (18/21) of stage III, and 95.9% (70/73) of stage IV pancreatic cancers (Klein et al. 2021).

In terms of screening for PDAC in the high-risk group of NOD, the low prevalence of PDAC at approximately 1% in this group represents a significant barrier, necessitating the further enrichment of this group for PDAC. Biomarker-based stratification of individuals with NOD into high or low risk for PDAC, based on whether diabetes is secondary to pancreatic disease (type 3c diabetes mellitus, T3cDM), or the more prevalent T2DM is being explored as a means of enriching for PDAC-related DM. The precise prevalence of T3cDM amongst individuals with DM is not known, although various estimates, depending on study design have been reported (Ewald et al. 2012; Vujasinovic et al. 2013; Woodmansey et al. 2017). Briefly, in a study of 1,868 patients diagnosed with DM who were admitted to hospital in Germany, reclassification of their DM according to the American Diabetes Association identified 172 patients (9.2%) that could be classified as having T3cDM (Ewald et al. 2012). Of 150 patients with DM in a single center in Slovenia, the prevalence of exocrine pancreatic insufficiency was found to be 5.4% (Vujasinovic et al. 2013). In a third study, when a cohort of 31,789 new diagnoses of adult onset diabetes in primary care in the United Kingdom was examined for pre-existing pancreatic disease, 559 individuals (1.75%) had a diagnosed pancreatic disease which preceded their diagnosis of diabetes (Woodmansey et al. 2017). This study differs from the previous two in that no attempt at reclassification of diabetes status of the whole cohort was made. We recently reported that the combination of two blood-based proteins, adiponectin and interleukin-1 receptor antagonist (IL-1Ra) showed strong diagnostic potential (AUC of 0.91; 95% CI: 0.84–0.99), for the distinction of T3cDM from T2DM (Oldfield et al. 2022). More work will be required using pre-diagnostic NOD cohorts to determine whether biomarker-based stratification of this high-risk group, based on the subtype of diabetes, will facilitate PDAC detection earlier.

There are numerous additional new approaches being taken to detect PDAC early. Here we list a small selection of recent advances. Ferguson et al. (2022) explored whether the diagnostic accuracy of single PDAC tumor cell-derived extracellular vesicles (EVs) could be improved by detecting mutated cancer proteins in them. Having optimized single-EV analysis (sEVA) using model lines, the authors were able to detect vesicles in 15 of 16 stage I pancreatic cancer patients. This work provides an important proof-of-concept that sEVA may become a useful method for earlier detection of pancreatic cancer.

The evidence that microbiota contribute to gastrointestinal cancer initiation, disease progression and treatment response is persuasive (Johnston and Bullman 2022). This has led researchers to investigate the potential for alterations in an individual's microbiome to facilitate PDAC diagnosis (Kohi et al. 2022). Using secretin-stimulated duodenal fluid, Kohi et al. examined bacterial and fungal profiles from patients undergoing duodenal endoscopy (Kohi et al. 2022). In a total of 308 patients, including 74 with PDAC, 98 with pancreatic cysts, and 134 with normal pancreata, the group reported that patients with PDAC had higher levels of microbial DNA but lower microbial diversity compared to control subjects. While encouraging, additional work is required, including using pre-diagnostic samples, to address whether duodenal microbiome profiles could aid stratification of PDAC risk in individuals under surveillance for PDAC.

The potential for gut and oral microbiota to identify PDAC have recently been investigated (Kartal et al. 2022; Nagata et al. 2022). Undertaking shotgun metagenomics and 16S rRNA amplicon sequencing of fecal and saliva samples from Spanish PDAC patients and controls, Kartal et al. identified a fecal classifier comprising 27 microbial species that showed accuracy for discriminating PDAC from controls. This and other classifiers performed equally well in a German validation cohort (Kartal et al. 2022). Similarly, Nagata et al. trained fecal and saliva metagenomics data from a Japanese cohort to discriminate PDAC patients from control individuals, deriving signatures including 30 gut and 18 oral species, associated with PDAC (Nagata et al. 2022). In validation studies, based on the Spanish and German cohorts mentioned above (Kartal et al. 2022), these signatures performed well in distinguishing PDAC. Of note, in all three cohorts Nagata et al. reported significant enrichments in the PDAC gut signatures of Streptococcus and Veillonella spp and a depletion of Faecalibacterium prausnitzii (Nagata et al. 2022). Taken together, these studies provide promise that fecal and salivary microbiota may contribute to early detection protocols for PDAC.

Advances in artificial intelligence provide automated tools for capturing unique features in medical images that may not be perceptible to the human eye. Qureshi et al. undertook radiomic analysis of abdominal computed tomography (CT) scans taken prior to PDAC diagnosis, identifying features predictive of PDAC. This led to a classifier, trained to perform automatic classification of CT scans into healthy control or prediagnostic. The average classification accuracy on an external dataset was 86% (Qureshi et al. 2022).

Predictive and Prognostic Biomarkers

Management of patients with pancreatic cancer is facilitated by any factor that can be used to predict outcome prior to treatment. This has been and will continue to be based on a clinical evaluation of the patient and their tumor. The assumption that patients with a larger more invasive cancer will survive for less time than a patient with a smaller localized cancer is supported by a mass of empirical evidence, nevertheless determining prognosis is considerably more complex than determining stage, also accurately determining stage in a patient prior to surgical intervention is not always an easy task. The PET-PANC study confirmed the benefit of conventional FDG-PET in staging cancers (Ghaneh et al. 2016), but although this is unquestionably a biomarker study, we will avoid discussion of PET and other forms of imaging (as these will be dealt with elsewhere). Similarly, grade of the tumor is a determinant of prognosis and histopathological assessment of grade is critical in giving an evaluation of prognosis in adjuvant therapy and increasingly following targeted biopsy in patients with advanced disease, but again this is a topic for another chapter (Chapter 20). Here we will only consider surrogate markers of grade, stage, and the level of residual disease subsequent to surgery or first line therapy (Figure 2).

Prognostic Biomarkers

Prognostic Serum Markers

Serum levels of particular proteins or antigens (such as CEA, PSA, alpha-fetoprotein, CA125) have long aided the diagnosis of cancers. For PDAC, the most widely used marker is CA19-9. CA19-9 levels are predictive of disease stage, resectability, progression, recurrence, and survival (Hartwig et al. 2011; Ko et al. 2005). Perioperative levels correlate with disease stage, and postoperative reduction (or levels <200 U/ml) in CA19-9 is an independent predictor of survival in resectable cases (Ferrone et al. 2006; Humphris et al. 2012). CA19-9 kinetics are a strong predictor of response to treatments (Luo et al. 2021). Postoperatively, CA19-9 levels <90U/ml can both predict favorable response to adjuvant chemotherapy, as well as guide the choice between FOLFIRINOX or gemcitabine (Luo et al. 2021). Evidence emerging from a large cancer database study in 28,000 patients (The National Cancer Database) showed stage dependent decrease in survival, and points to benefit from neoadjuvant chemotherapy in patients with pre-operative CA19-9 levels >37 U/ml (Bergquist et al. 2016). CA19-9 response in borderline resectable or locally advanced PDAC patients receiving neoadjuvant therapy, can guide chemotherapeutic switch and its duration improving post-operative disease outcomes and patient survival (Truty et al. 2021). Furthermore, as demonstrated in a key study (MPACT trial) comparing systemic therapies in metastatic PDAC, CA19-9 decline eight weeks into treatment indicates a chemotherapeutic efficacy, which can help in evaluating prognosis or even in suggesting a need for a change in therapy (Chiorean et al. 2016).

Non-cancer Prognostic Markers

Prognosis is determined by the nature of the cancer, but also by the patient who developed the cancer. Performance status measures including the Eastern Cooperative Oncology Group (ECOG) and Karnofsky (KPS) are undoubtedly biomarkers, and are central factors in prognostication, choice of treatment, and care and patient inclusion in clinical trials, but here only surrogate markers of performance will be considered. These include markers of sarcopenia, gut dysbiosis, aging, and immunological response. Imaging techniques such as Dual Energy X-ray Absorptiometry (DEXA) can be used to measure changes longitudinally and relate them to cachexia and so to prognosis (Cole et al. 2020). Similarly measures of immune response and inflammation such a CRP (Laird et al. 2016) or Neutrophil Lymphocyte Ratio (NLR) (Barker et al. 2020) are also related to cachexia and hence prognosis. The immunological capacity of a patient is both influenced and influences the gut microbiome, making dysbiosis in this compartment an attractive biomarker (Guo et al. 2022). Age is a well-known prognostic factor in pancreatic cancer, although this might be due to different management approaches in elder patients (van Dongen et al. 2022) but aside from chronological age, it also appears that markers of biological age such as GDF15 relate not just to the risk of cancer but also to its prognosis (Basisty et al. 2020).

Molecular Predictors of Prognosis

Cancer is fundamentally a genetic disease determined by the genome of the cancer cells and their interaction with the soma of the patient, impacting on the expression patterns of the whole tumor (cancer and stromal cells). Tissue transcriptomic

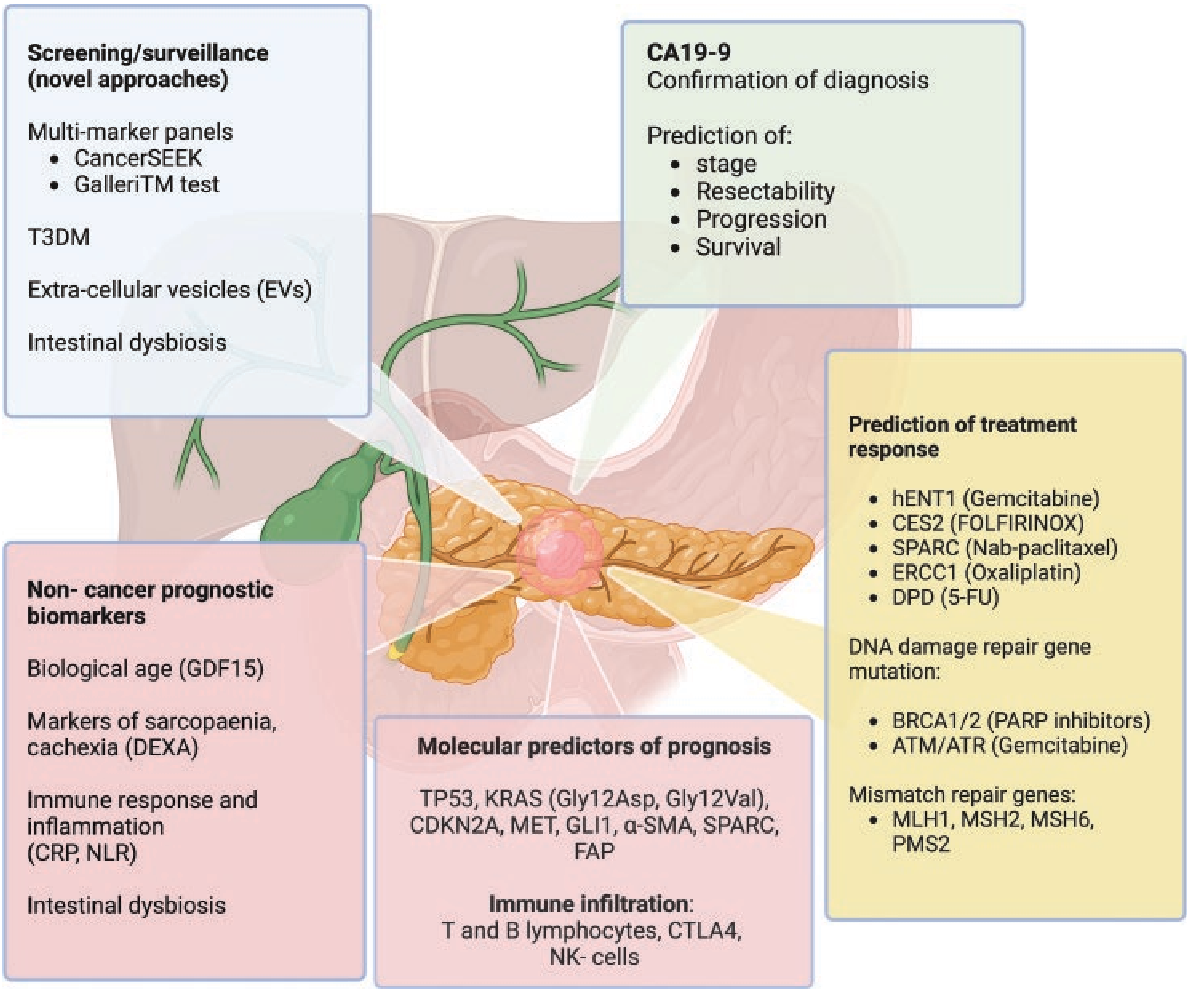
Screening/surveillance (novel approaches)
Multi-marker panels
• CancerSEEK
• GalleriTM test
T3DM
Extra-cellular vesicles (EVs)
Intestinal dysbiosis
CA19-9
Confirmation of diagnosis
Prediction of:
• stage
• Resectability
• Progression
• Survival
Prediction of treatment response
• hENT1 (Gemcitabine)
• CES2 (FOLFIRINOX)
• SPARC (Nab-paclitaxel)
• ERCC1 (Oxaliplatin)
• DPD (5-FU)
DNA damage repair gene mutation:
• BRCA1/2 (PARP inhibitors)
• ATM/ATR (Gemcitabine)
Mismatch repair genes:
• MLH1, MSH2, MSH6, PMS2
Non- cancer prognostic biomarkers
Biological age (GDF15)
Markers of sarcopaenia, cachexia (DEXA)
Immune response and inflammation (CRP, NLR)
Intestinal dysbiosis
Molecular predictors of prognosis
TP53, KRAS (Gly12Asp, Gly12Val), CDKN2A, MET, GLI1, α-SMA, SPARC, FAP
Immune infiltration:
T and B lymphocytes, CTLA4, NK- cells

Figure 2 A summary of evolving biomarkers for screening/surveillance, prognostication, and prediction of treatment response in pancreatic cancer. CA19-9 is the only clinically approved biomarker used for confirmation of diagnosis and prediction of stage, resectability, and monitoring of disease progression.

studies have led to an evolving classification of pancreatic cancers (Bailey et al. 2016). Puleo et al. carried out RNA-sequencing of formalin fixed paraffin embedded tissue. The authors described 5 PDAC subtypes by integrating genomic data from the neoplastic, stromal and immune compartments (Puleo et al. 2018); **Pure basal like** (higher in mutations of *CDKN2A* and *TP53*, with *KRAS* Gly12Asp, Gly12Val mutations and with greater metastatic spread along with scarce stroma), **stroma activated** (higher MET and nuclear GLI1 expression suggesting increased hedgehog signaling; also increased α-SMA, SPARC and FAP), **desmoplastic** (higher levels of CTLA4, increased number of T-cells, more inflammatory and vascular marker with lower tumor cell content), **pure classical** (characterized by KRAS Gly12Arg mutation, with high levels of human equilibrate transporter 1; hENT1 and highly stromal), and **immune classical** (marked stroma, NK-cells, T and B lymphocytes, CTLA4 expression and low proteasome/apoptotic signals) (Puleo et al. 2018). Survival was associated with subtype; basal like (median OS 10.3 months), stroma activated (median OS 20.2 months), desmoplastic (median OS 24.3 months), immune classical (median OS 37.4 months) and pure classical (median OS 43.1 months).

Predictive Biomarkers

Contrasting Prognostic and Predictive Biomarkers

Therapeutic benefit is shown when individual patients survive longer with treatment than without it. It is therefore easier to demonstrate benefit in a patient with a very poor prognosis without treatment than in a patient who would have a good prognosis regardless of treatment. Therefore, far from being equivalent to prognostic biomarkers, it is easier to show that a marker is predictive if it is inversely prognostic in the absence of the specific treatment. It is therefore surprising that hENT1 (Human Equilibrative Nucleoside Transporter 1) expression has been shown to be more highly expressed in the pure classical subtype described above, as high expression of this protein was shown to be associated with better survival in patients treated with gemcitabine than patients treated with 5FU (at least partly due to poor prognosis in patient with high expression of this protein when given alternative treatments) (Aughton et al. 2021).

Predicting Predictive Biomarkers

Empirical identification of biomarkers that predict benefit of one therapy over another is difficult, so in most cases specific candidates are examined based on their theoretical relationship to the treatments being investigated. For example, high levels of a protein that is known to activate a particular pro-drug would be expected to benefit the use of that pro-drug, while high levels of the target of a particular drug would be expected to make that drug less effective (simply on the basis that more of the drug would have to reach the cancer cell to allow inhibition of the target).

Choice of Chemotherapy

Targets and Drug Metabolism

As mentioned above the tumor cell levels of the nucleoside transporter hENT1, which transports gemcitabine into pancreatic cancer cells has been shown to benefit the use of gemcitabine over a nucleobase therapy (5-FU) (Greenhalf et al. 2014). The rationale for testing this specific hypothesis is clear (although, the fact that hENT1 also transports gemcitabine out of cancer cells is often forgotten). Similarly, the rationale for examining the effect of expression of the target of gemcitabine (ribonucleotide reductase) is clear, but in this case the hypothesis that high levels would mean gemcitabine was less effective had to be rejected (at least in cells with low levels of hENT1) (Elander et al. 2018). Another clear hypothesis was that the protein cytidine deaminase (CDA), which metabolizes and so potentially eliminates gemcitabine, should be associated with a low level of response to that drug. Again, this was not seen when the levels of the protein were examined, although when the levels of the transcripts of CDA and hENT1 were examined these were found not to relate to the levels of their respective proteins and in the case of CDA, where CDA transcript levels were high, the benefit of high hENT1 protein was found to be lost, put another way, the benefits of hENT1 on gemcitabine response were only seen in patients with low levels of CDA transcript even though the low transcript levels were not reflected in low levels of the protein (Aughton et al. 2021).

The majority of patients who have unresectable and metastatic PDAC disease, which accounts for ~50% of patients with PDAC, are often placed on a Gemcitabine-based chemotherapy, like Gemcitabine and nab-paclitaxel (Abraxane®). FOLFIRINOX is also a commonly utilized form of chemotherapy, used to treat good performance status patients with PDAC (as discussed elsewhere), certainly in patients with good performance status (Conroy et al. 2018). To be of use, a predictive biomarker applied to most patients would therefore have to indicate that an alternative treatment would be of more benefit (or of less harm) than FOLFIRINOX. Applying the same rationale as above for gemcitabine, based on the known action of the drug, is complicated by the fact that FOLFIRINOX is a combination therapy: 5-FU, Irinotecan and Oxaliplatin, all having different modes of action. With respect to irinotecan, high expression of the prodrug metabolic enzyme carboxylesterase-2 (CES2) would obviously give greater sensitivity to the prodrug, and certainly there is an association between sensitivity to irinotecan and level of expression of CES2 in cell lines, with knockdown of CES2 having the predictable effect of increasing resistance to irinotecan (Capello et al. 2015).

However, it is far from evidence that a tumor with high levels of CES2 would be more sensitive to irinotecan, let alone that this would mean that CES2 levels would predict response to the combination of drugs in FOLFIRINOX, particularly in the context of adjuvant therapy where its expression levels would relate to cells already removed from the patient. Control of CES2 expression is at least in part dependent on the level of expression of hepatocyte nuclear factor 4 alpha (HNF4A), which in turn is upregulated in patients with diabetes mellitus (DM). Thus, PDAC patients with DM have higher levels of CES2, so it is reasonable to assume cancers would have greater sensitivity to irinotecan. A mechanism maintaining this even once the cancer cells are excised from the patient is supported by greater irinotecan sensitivity of patient derived xenografts with higher CES2 levels. This does not mean that patients with DM respond better to FOLFIRINOX or even that patients with higher levels of CES2 respond better, but it is supportive of that hypothesis. To date CES2 association with prognosis in patients has been supported (albeit in relatively small numbers of patients) but proof that this is dependent on the choice of FOLFIRINOX as a treatment option has yet to be provided (Capello et al. 2020).

For oxaliplatin, no prodrug activation is required and theoretically the key determinant of sensitivity (as with all platinum based agents) is capacity to carry out nucleotide excision repair. Sadly, when levels of enzymes involved in this pathway (e.g. ERCC1) have been investigated, no predictive value has been established in patients with pancreatic cancer (Tezuka et al. 2018).

Similarly, for Gemcitabine with nab-paclitaxel (Abraxane®) as an alternative to FOLFIRINOX, the hoped for (and theoretically plausible) association of response with accumulation of albumin-bound drugs, linked to the expression level of Secreted Protein Acid and Rich in Cysteine (SPARC), was investigated and shown not to be adequate for use as a biomarker (Ormanns et al. 2016).

Efficacy of a drug is not only determined by susceptibility of cancer cells to the agent, but also (and inversely) by sensitivity of the recipient's healthy cells to that agent. Hence, although cancer cell expression of DihydroPyrimidine Dehydrogenase (DPD) would be expected to reduce the effectiveness of 5-FU as it metabolizes and clears this agent, an inverse relationship would be predicted between DPD expression in non-cancer cells, given that reduced levels would increase toxicity of the drug. Cancer cell DPD levels proved ineffective as a biomarker (Elander et al. 2018), but germline genotypes of up to 9% of patients, which give low DPD expression do result in higher toxicities and therefore poor prognosis (Wörmann et al. 2020).

Semi-empirical Biomarker Selection

There are pathways and processes that, while not specific to any particular agent, are clearly related to an effective response to chemotherapy. For example, rate of cell cycle progression, ability to carry out apoptosis, level of inflammation, and capacity for DNA repair. A cancer that is poor at DNA repair would be predicted to respond better to a DNA damaging agent, conversely a patient who is poor at DNA repair due to germline deficiency might be predicted to suffer greater toxicity with such an agent. An agent that relies on patient's immune response will be more likely effective in a patient with an unimpaired immunogenic capacity or against a particularly immunogenic cancer. Agents that work through apoptosis will be most effective against cancers where key elements of the apoptotic pathways are intact. Finally, agents that work by killing dividing cells will be most effective where cancer cells have a high turnover.

DNA Damage Repair Gene Mutations

PDAC can be subtyped ("stable," "locally rearranged," "scattered," and "unstable") based on genomic alterations and variation in chromosomal structure (Waddell et al. 2015). DNA damage repair (DDR) gene mutations commonly associated with the "unstable" molecular subtype include that carry out Homologous DNA Repair, generally Fanconi anemia pathway genes (e.g. *BRCA1/2* and *PALB2*) and genes involved in signaling the presence of DNA damage (e.g. *ATM/ATR*). Mutations in these genes can be both germline and somatic in PDAC (Perkhofer et al. 2021). The unstable group of patients would be predicted to respond better to DNA damaging agents such as FOLFIRINOX (Froeling et al. 2021). More specifically, deficiency in homologous DNA repair of double strand breaks would make cells more sensitive to agents that target other forms of repair and so increase the chance of double strand breaks forming. Hence in patients who have germline mutations in *BRCA1* or *BRCA2* their cancer cells are more sensitive to inhibitors of the proteins PARP1/PARP2 which are involved in base excision repair and other forms of single strand DNA repair (Bryant et al. 2005). Maintenance treatment using PARP inhibitors (such as Olaparib) have shown clinical efficacy in ovarian, breast, and metastatic pancreatic cancer on a background of BRCA germline mutations. Most significantly, the efficacy of Olaparib as a maintenance therapy was recently assessed in the phase III POLO (Pancreas Cancer Olaparib Ongoing) trial, which demonstrated extended progression free survival (7.4 months vs 3.8 months for the placebo group) in germline *BRCA1/2* mutated, metastatic PDAC (Golan et al. 2019).

Notably, the established clinical benefit has so far been restricted to germline *BRCA* mutations. Up to 7% of PC patients harbor germline BRCA mutations (Golan et al. 2019); loss of homologous DNA repair probably occurs earlier in tumorigenesis in such patients and so will be more homogeneous in the cancer, which may explain why inherited mutations result in the most obvious benefit from PARP inhibition. Other inherited mutations in DNA repair genes include pathogenic mutations in mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2*). Germline mutations in these genes cause Lynch syndrome, which is most associated with a hereditary predisposition to colon cancer, but also increase the risk of PDAC, MLH1 mutation being associated with a 7.8 relative risk of PDAC (Bujanda and Herreros-Villanueva 2017). The MMR proteins function to maintain genomic stability by repairing base-base mismatches or insertion/deletion mis-pairs following DNA replication and recombination. DNA mismatches commonly occur in regions with repetitive nucleotide sequences (microsatellites); loss of function of the MMR proteins results in accumulation of mononucleotide errors, causing microsatellites to change length (i.e. demonstrate instability).

Pancreatic cancer is generally not associated with microsatellite instability and is not associated with sensitivity to checkpoint inhibitor treatment. However, MSI is associated with better response to immunotherapy, presumably because of a greater mutational burden in the cancers (Ganesh et al. 2019). So, it is reasonable to assume that PDAC in Lynch syndrome families would be more responsive to checkpoint inhibitors (Kubo et al. 2022).

The ATM protein, like the ATR protein binds to double strand DNA breaks and signals to cause cell cycle arrest and DNA repair. Biallelic pathogenic variants in the ATM gene result in ataxia telangiectasia, a syndrome including telangiectasia of the skin, cerebellar ataxia, and immunosuppression. Affected individuals present in the first decade of life and have a 38% risk of cancer over their lifetime, including a 2.4-fold increased risk of PC (Geoffroy-Perez et al. 2001; Thompson et al. 2005). There is some evidence that PDAC with mutant ATM is more sensitive to gemcitabine, consistent with gemcitabine inhibiting ribonucleotide reductase and hence promoting replication catastrophe through nucleotide starvation (Dunlop et al. 2020).

Inflammation, Apoptosis, and the Cell Cycle

While biomarkers of DNA repair defects have proved to be promising predictive biomarkers (at least with germline mutations) markers of apoptosis and cell cycle progression have proven more effective as prognostic markers than predictive markers. A mutation in *TP53*, for example, will make a cell more resistant to gemcitabine (Fiorini et al. 2015) as it is more difficult to induce apoptosis, but it will similarly reduce the sensitivity to FOLFIRINOX or any other chemotherapy, so it is of limited predictive value when selecting a therapy. Similarly, inflammatory markers may associate with worse survival in patients treated with irinotecan, there is as yet no evidence that better survival would be seen with alternative treatments (Merz et al. 2020).

Predicting Response to Novel Agents

To date chemotherapy remains the mainstay of adjuvant, neoadjuvant, and palliative care. This is no doubt a consequence of the limited number of patients who will benefit from more targeted therapy, hence an inability to show benefit in an unselected group of patients. Predictive biomarkers could provide the necessary selection of necessity; this will require an even greater dependence on non-empirical methods to choose which markers to test. Fortunately, targeted therapy has (by definition) a clear target and equally clear candidate biomarkers.

Perhaps the most obvious target for treatment of pancreatic cancer is the near ubiquitous K-Ras mutations. These have proven remarkably difficult to exploit, but recently anti KRAS agents (sotorasib and adagrasib) have been FDA approved for treating KRAS G12C mutated tumors, although this variant constitutes only 3% of PDACs (Hong et al. 2020).

Predictive Biomarkers in Systemic PDAC Therapy

Predicting patient response to these agents in advance of therapy is therefore pivotal for optimizing clinical outcomes. Dihydropyrimidine dehydrogenase (DPD) is a key catabolic enzyme of 5-FU, and chemo resistance to this agent is seen with its upregulation, resulting in poor clinical response (Elander et al. 2018). Guidelines therefore recommend patient testing for DPD deficiency prior to treatment with 5-FU derivatives and capecitabin (Wörmann et al. 2020).

Biliary Tract Cancers

Introduction

Biliary tract cancers (BTCs) comprise a group of rare and highly heterogeneous malignancies associated with poor patient survival, and a poorly understood etiology (Banales et al. 2020; Tariq et al. 2019). Identifying key modifiable risk factors in BTCs is essential for predicting, treating, and preventing these cancer types (Valle et al. 2017). BTCs are defined as epithelial malignancies of the biliary tract and include cancers of the gallbladder (GBC), cholangiocarcinoma (CCA) or bile duct cancer, affecting intrahepatic (iCCA) or extrahepatic bile ducts (eCCA), and the ampulla of Vater (AVC) (Jackson et al. 2019).

BTC incidence varies by geographic regions, with the highest incidence observed in Chile (14.35) and the lowest in Vietnam (1.25) (Baria et al. 2022). BTCs occur more commonly in South-East Asia, due to the increased incidences of parasitic diseases including liver flukes Opisthorchis viverrini (OV) and Clonorchiasis sinensis (CS) infestations in those zones (particularly in north-east Thailand and China) where BTCs (specifically CCA) are more prevalent (Sithithaworn et al. 2012). However, overall, GBC is the most common cancer of the biliary tract (2.2 cases per 100,000 worldwide) although incidence varies globally (Mahdavifar et al. 2018; Marcano-Bonilla et al. 2016). The incidence of BTC in high-income countries are about 0.35–2 cases per 100,000 annually; however, in endemic regions of Thailand and China its incidence increases up to 40-fold (Izquierdo-Sanchez et al. 2022; Valle et al. 2021). A higher prevalence is observed in certain regions (South America and southern Asia) where cholelithiasis is more prevalent and linked with the development of GBC (Hundal and Shaffer 2014). The incidence of GBCs is lower in western Europe and the USA (1.6–2.0/100,000) and in high-risk countries (e.g., Chile and India) the incidence reaches 24.3/100,000 in females (and 8.6/100,000 in males) (Rawla et al. 2019). Overall, the incidence of BTCs is higher in males than in females (Baria et al. 2022).

Currently, CCA is the second most common type of primary hepatic malignancy, accounting for an estimated 15% of all primary liver tumors (Sung et al. 2021). CCA contributes roughly to 2% of all cancer-related deaths yearly. Epidemiological data suggests a constant rise in CCA incidence worldwide, being distinctly apparent in certain Western and Southeast Asian countries, with Asians having the highest incidence for both subtypes (Banales et al. 2016). Worldwide, the highest CCA incidence rate is found in Thailand (113/100,000 in males, and 50/100,000 in females). Globally, CCA has an incidence rate of 0.3–6/100,000 inhabitants per year (Ledbetter and Hotchkiss 1975). Studies have reported differences in the trends in incidence among iCCA and eCCA, as iCCA is seen to be on a steady rise, whereas eCCA displays a more stable incidence rate (Brindley et al. 2021; Khan et al. 2019).

Etiology and Risk Factors

The etiology of BTCs is complex and remains poorly understood. Main risk factors are common among BTCs (Table 1). Presence of gallstones is the strongest risk factor for GBC and is also relevant to CCA development (hepatolithiasis) (Kirstein and Vogel 2016). Other risk factors include porcelain

Table 1 Summary of risk factors and high-risk groups linked with the development of pancreatic and biliary tract cancers.

Risk factor	**Pancreatic cancer**	BTC
Lifestyle	*Modifiable* Smoking Alcohol Obesity Dietary • High fructose diet • Red meat • Processed meats *Non-modifiable* Age	*Modifiable* Smoking Alcohol Obesity Dietary • Low fiber diet • Raw fish • Red meat • Processed meats
Genetic predisposition	*Germline mutations*: • *BRCA1/2 (HBOC)* • *KRAS* • *PALB2* • *CDKN2A* • *ATM* • *APC* • *MLH1/MSH2, MSH2, MSH6 (Lynch Syndrome)* • *TP53 (Li-Fraumeni syndrome)*	*Germline mutations*: • *BRCA1/2* • *KRAS* • *SMAD4* • *NF1* • *ATR* • *NF1* • *ARID1A* • *PBRM1* • *RAD51D* • *MUC17* • *MLH1/MSH2* • *TP53*
Environmental, occupational	Pesticides Aromatic Hydrocarbons Heavy metals	Toxins • Aflatoxin *(Aspergillus spp)* • Ochratoxin A *(Aspergillus spp)* Parasitic infections • *O. viverrine* • *C. sinensis* Viral infections • Hepatitis B virus (HBV) • Hepatitis C virus (HCV) Bacterial infections • *Salmonella spp* • *H. pylori*
High risk groups	Familial Pancreatic Cancer Hereditary Caner Syndromes • Peutz-Jeghers Syndrome *(STK11)* • Hereditary pancreatitis *(PRSS1)* Pancreatic Cysts • IPMNs • MCNs New-Onset Diabetes (NOD)	Primary Sclerosing Cholangitis (PSC) Liver fluke Endemic regions • *(O. viverrini, C. sinensis)* High risk occupation • Rubber, dye industry • Agriculture (pesticides)
Anatomical, abnormalities		Gallbladder polyps Caroli's disease Gallstones, hepatolithiasis Porcelain gallbladder

spp: Species; NOD: New Onset Diabetes.

gallbladder, gallbladder polyps, benign biliary disorders associated with chronic inflammation (such as primary sclerosing cholangitis (PSC) for CCA), chronic infection (e.g. salmonella typhi), liver diseases (cirrhosis due to other causes, hepatitis C), congenital malformations such as choledochal cysts and biliary papillomatosis, family history (risk increases if multiple first-degree relatives had the disease), and genetic alterations (e.g. mutations in *TP53, KRAS, CDKN2A, IDH1/2, FGFR2* fusions). Apart from geographically associated risks, there are some other risk factors associated with an increased risk of developing BTCs which are a bit more controversial, including: age, metabolic disorders (diabetes, obesity), smoking, and alcohol abuse (Labib et al. 2019). However, in the case of CCA, the vast majority of cases (around 70%) develop sporadically without any known underlying disease (Brindley et al. 2021; Izquierdo-Sanchez et al. 2022; Khan et al. 2019).

Infectious Diseases

Parasitic Infections

Certain systemic infections involving parasites, bacteria, and viruses play a pivotal role in the development of BTC through longstanding inflammation within the biliary tract. There is a strong association between *Opisthorchis viverrini* (OV) and *Clonorchiasis sinensis* (CS) liver fluke infestations and the development of biliary tract malignancies (Prueksapanich et al. 2018). There is a consistently high incidence of CCA in endemic regions including Asia and North-Eastern Europe areas with an incidence of 85 per 100,000 population (Chaiteerakij et al. 2017). *O. viverrini* infection, is endemic to northeast Thailand, Laos, and Cambodia, whereas China, Taiwan, Korea, and Vietnam are endemic areas for *C. sinensis*, both which are risk factors most strongly associated with development of CCA (Khan et al. 2019). The consumption of raw or undercooked wild-caught cyprinoid fish (which host these parasites) leads to infestation with these liver flukes which drive an inflammatory process whilst occupying the biliary tree and the gallbladder (Moeini et al. 2021; Phyo Myint et al. 2020). These flukes secrete oncogenic metabolites into circulating bile which are inflammatory as they induce desquamation of the biliary epithelium, ductal fibrosis, and adenomatous hyperplasia formation within biliary ducts which precedes dysplasia and biliary carcinoma (Cardinale et al. 2018). Evidence of fluke-induced host inflammatory response within biliary ducts is evident through the expression of Opistorchis and Clonorchiasis antigens in circulating peripheral macrophages and epithelioid cells of the host's immune systems (Brindley et al. 2021). Subsequent to epithelial injury and an immune response against these parasites, pro-inflammatory cytokines and transforming growth factors activate fibroblasts, and proteases and metalloproteinases are released (which induce changes in the extracellular matrix and oxidative stress) leading to further injury and fibrosis of the biliary tract. This is the initial step in a multistep process that involves the transformation from hyperplasia to dysplasia and eventually carcinogenesis (Sala et al. 2020; Zhao et al. 2021).

Viral Infections

The persistent infection with Hepatitis B (HBV) and Hepatitis C (HCV) viruses contributes to the pathogenesis of BTC. The prevalence of chronic viral infections coincides with the highest prevalence of CCA, which we see in Southeast Asia when compared to Western countries (UK, USA, Denmark, Norway, and the Czech Republic) (Wang et al. 2017). The prevalence of HBV and HCV in southeast Asia is 9.1% and 3.6% respectively; when looking at specific countries in this region, China (HBV 12%; HCV 3%), and Korea (HBV 12%; HCV 2%) were all higher when compared to western counterparts (Alberts et al. 2022). Multiple studies have highlighted that chronic HCV infection increases the risk of iCCA by two-fold (HR: 2.6; 95% CI: 1.3–5.0) (Marcano-Bonilla et al. 2016) and that HCV infection is associated with a six-fold odds ratio (OR) increase in developing iCCA, whilst eCCA risk is unchanged (Clements et al. 2020). When assessing the risk associated with chronic HBV, there is a clear increased risk of developing iCCA (RR: 3.4; 95% CI: 2.5–43.7) when compared to those without HBV (Fragkou et al. 2021; Marcano-Bonilla et al. 2016). A meta-analysis looking at the prevalence of HBV in regions of both high and low incidences of hepato-pancreaticobiliary malignancies, concluded that chronic HBV infection was associated with an increased risk for iCCA (Bridgewater et al. 2014). The association between HBV and CCA was stronger in Asian countries (OR: 6.0) compared to Western countries (OR: 4.0) (Marcano-Bonilla et al. 2016). Cirrhosis subsequent of HBV or HCV persistent infections increases the risk for iCCA, by 3-fold in HBV patients, and 3.2-fold in HCV patients (Pinter et al. 2016). In co-infections with both HBV and HCV and an established cirrhosis, the risk of iCCA significantly increases to just over 10-fold, hence there is a clear and strong association between viral hepatitis and CCA (Wang et al. 2017).

Bacterial Infections

Certain bacterial infections of the biliary system occur due to translocation through disruptions of the intestinal mucosa (Masia and Misdraji 2018). Bacterial pathogens like Salmonella enterica subspecies, including *S. typhi*, a gram-negative bacterial pathogen, can spread to the gallbladder via the vasculature or through the bile ducts from the liver via the enterohepatic circulation (Sharma et al. 2022). Several studies have shown that chronic carriers of *S. typhi* have an increased risk of GBC (Gunn et al. 2014; Koshiol et al. 2016). The presence of chronic bacterial infection of similar bacterial pathogens such as the above permits chronic and persistent inflammation of the biliary epithelium, which can often potentiate carcinogenesis within the biliary epithelia through initial hyperplasia, then dysplasia and to the development of either GBC or other BTCs (Espinoza et al. 2016).

Helicobacters are gram-negative bacteria with a characteristic helical shape which can act as an infectious carcinogen. Specific species of helicobacter have been identified within the GI tract and biliary tract systems in certain hepatobiliary diseases (Kusters et al. 2006). Similar to the pathogenesis of biliary and gallbladder malignancies with *S. typhi* as the infectious carcinogen, studies have shown that *H. pylori* behaves like *S.typhi* in the development of biliary and gallbladder malignancies through the promotion, propagation, and maintenance of inflammation, development of hyperplasia of biliary epithelial cells which can then develop into dysplasia and eventual biliary malignancy (Cherif et al. 2019). Virulence factor CagA *which is produced by H. pylori* is an oncoprotein that interferes with signal transduction pathways including activation of the nuclear factor kappa B (NF-κB) signaling pathway. NF-κB signaling induces cellular expression of the pro-angiogenic vascular endothelial growth factor (VEGF) which is implicated in BTC and GBC development (Ito et al. 2020; Stein et al. 2013). The oncoprotein also promotes the host immune response to Helicobacter antigens in the form of an inflammatory response with a milieu of cytokines and other inflammatory mediators (Segura-López et al. 2015). Numerous studies have supported the conclusion of clear associations between *H. pylori* and the development of hepatobiliary cancers, including BTCs and GBCs (Makkar et al. 2020).

Biliary Tree Structural Abnormalities

Certain anatomical defects are also associated with an increased risk for CCA and GBC. Choledochal cysts (bile-filled sacs along the common bile duct) and Caroli's disease (rare congenital fibro-polycystic dilations within the large intrahepatic bile ducts) both contribute to the increased risk of the development of iCCA (Jabłońska 2012; Ye et al. 2022). Caroli's disease increases the risk of developing CCA by 100-fold when compared to the general population (Fahrner et al. 2020). In respect to cases of congenital choledochal cysts, these cysts often develop in an abnormal pancreaticobiliary junction (APBJ) in 90% of cases of congenital choledochal cysts. The APBJ is a rare anatomical variation, this results in the main pancreatic duct draining directly into the common bile duct (Baison et al. 2019). This can potentiate chronic and prolonged exposure and irritation of the biliary epithelium by pancreatic juice (which contains digestive enzymes including trypsinogen, elastase, carboxypeptidase, lipases, amylase) (Kamisawa et al. 2017). The resulting chronic inflammation promotes the carcinogenesis of both GBC and BTCs. Studies identified however that APBJs more commonly underly cases of GBC than CCA (Hu and Lim 2022).

Gallstones and Hepatolithiasis

Gallstones are a common risk factor for the development of GBC. Cholesterol and pigment gallstones are synthesized within the gallbladder and can cause chronic inflammation via chronic cholecystitis, although the exact mechanism by which gallstones predispose GBC is still unknown. About 80% of people with GBC present with gallstones during diagnosis, however, the majority of patients with gallstones do not develop GBC (Stinton and Shaffer 2012). The association of gallstones with CCA is less well established than the association of gallstones with GBC, however, the association of bile duct stones or hepatolithiasis with CCA is quite strong and can be due to chronic inflammation of the bile duct (Kirstein and Vogel 2016). Hepatolithiasis is a well-known associated risk factor for CCA development, particularly in parts of South-East Asia (Kim et al. 2015). Studies have highlighted that one of the highest associated risks between CCA and hepatolithiasis is in Japan (Cardinale et al. 2010). Hepatolithiasis are caused by persistent portal bacteremia and associated vessel phlebitis. Their presence leads to obstruction of the intrahepatic biliary ducts causing bile stasis and reflux, therefore increasing the risk of cholangitis and bile stricture formation (Jarnagin and Winston 2005). This chronic inflammatory process drives the development of CCA (Khan et al. 2019).

A recent 30-year follow-up study concluded that BTC risks were significantly higher in patients who had both gallstones and cholecystitis, in regards to developing GBC (OR = 34.3, 95% CI 19.9–59.2) (Hsing et al. 2007). The type of gallstone can delineate the likelihood of the occurrence of either BTC or GBC. A study underlined that patients with bile duct cancer were more likely to have pigment stones, and patients with GBC to have cholesterol stones (Portincasa et al. 2019). Overall, gallstones were associated with a higher risk of cancers of the hepatopancreaticobiliary system.

Porcelain Gallbladder

The porcelain gallbladder is associated with an increased risk of developing GBC. A porcelain gallbladder is a condition whereby the wall of the gallbladder becomes covered with calcium deposits. This can also occur as a result of chronic recurrent cholecystitis caused by gallstones (Calomino et al. 2021). Patients with porcelain gallbladder have a higher risk of developing gallbladder cancer likely due to persistent inflammation associated with the pathogenesis in the development of this condition (Morimoto et al. 2021).

Gallbladder Polyps

A gallbladder polyp is essentially an exophytic growth from within the inner surface of the gallbladder wall. The constituents of some of the polyps are directly formed from cholesterol deposits lining the gallbladder wall, some of the polyps are derived from inflammation, and the remaining polyps are a benign or malignant aggregation of biliary epithelium (Andrén-Sandberg 2012). Large polyps (>1cm) are likely to be cancerous and often the recommendation is for cholecystectomy for polyps of this size or larger (Kalbi et al. 2021).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), is the most well-known associated risk factor concerning CCA. PSC is an autoimmune liver condition characterized by inflammation of the biliary epithelium lining the biliary tree (Rodrigues et al. 2018). This inflammatory process in the bile ducts is also known as cholangitis. Chronic inflammation of the ducts leads to fibrosis and stricturing of the bile ducts. During the disease arc, when the inflammation settles, the lining of the epithelium develops scarring which is the sclerosing aspect of the condition. Blockage in the biliary tree can lead to infections and to the accumulation of toxic bile acids. This repetitive disease process increases the risk of GBCs and BTCs. PSC is strongly associated with inflammatory bowel disease, usually ulcerative colitis (Banales et al. 2020). In Western countries PSC is the main risk factor leading to CCA (incidence 10 per 100,000 people versus 1 per 100,000 in Eastern countries). PSC is more common in men than in women, accounting for almost 66% of the cases, and the mean age at diagnosis is 30–40 years (Song et al. 2020). PSC patients have 150–400 times higher risk of BTC compared to the general population (Tan et al. 2022). Patients who have PSC-associated CCA are unsuitable candidates for surgical resection due to the potential of multifocal severe disease causing severe hepatic dysfunction (Saffioti and Mavroeidis 2021).

Genetic Polymorphisms

Genome profiling of BTCs has given us a better understanding of the carcinogenesis of these types of cancers and highlights the importance of the genetic component in the multifactorial pathogenesis of such complex heterogeneous diseases (Wardell et al. 2018). Genomic sequencing of BTC tissue samples has allowed the identification of somatic and germline drivers and the pathogenic germline variants of cancer-predisposing genes which allow clinicians to facilitate the classification of tumors and determine treatment strategy (Clark et al. 2019). Results from genomic sequencing showed that the most common mutated genes were identified as *TP53, KRAS, SMAD4, NF1, ARID1A* (chromatin remodeling), *CDKN2A/B* (cell cycle regulator), *PBRM1 (chromatin modulation)*, and *ATR* which were related to poor outcomes regarding patient survival. *FGFR2* fusions are almost exclusive to iCCA, which also features *IDH1/2* and *BRAF* substitutions, and MET amplifications with a low KRAS mutational frequency. ERBB2 amplification and PIK3CA/mTOR pathway aberrations are more frequent in CCAs and GBC (Bekaii-Saab et al. 2021; Bridgewater et al. 2016).

Some new studies have highlighted that a novel deletion of MUC17 at 7q22.1 has severely negatively impacted patients' prognosis (Casadio et al. 2021). Sequencing methods have also highlighted deleterious germline mutations of cancer-predisposing genes such as BRCA1, BRCA2, RAD51D, MLH1, or MSH2 in patients with BTC (Hu et al. 2018; Wardell et al. 2018). This highlights the importance of understanding the marked heterogeneity of BTC and identifying it as a key factor of the difficulty in the management of BTC Hence why the genetic findings can be useful in establishing diagnostic strategies and targeted treatment for BTCs (Athauda et al. 2020).

Environmental and Lifestyle

Toxins

Certain biological and chemical toxins have been linked to the pathogenesis of BTCs. Aflatoxin is a key toxin heavily associated with the development of cancers of the biliary system. Aflatoxin is a mycotoxin produced by *Aspergillus bacterium*, which is documented to often be located usually in warm, humid regions and can be found in common food types including cereals, nuts, milk, and certain meats (Benkerroum 2020). The hypothesis of aflatoxin in BTC carcinogenesis is down to recurrent exposure of the metabolites of aflatoxin stored within the bile and is in direct contact with the biliary epithelium of the biliary system (Awuchi et al. 2022). A case-control study found significantly more circulating aflatoxin metabolites in patients with GBC compared to population controls (OR: 13.0; 95% CI: 3.0–52.5) (Koshiol et al. 2017). Ochratoxin A (OTA), is similar to aflatoxin and has also been indicated in BTC pathogenesis (Heussner and Bingle 2015). OTA is primarily produced by *Penicillium* and *Aspergillus bacteria*, and is found in similar food types to aflatoxins. A Japanese study established a link between a large proportion of young patients (25–45 years) diagnosed with CCA (specifically iCCA lesions originating in the large intrahepatic bile ducts) to their employment in proof-printing plants (Kumagai et al. 2013). The causative link was due to their chronically high level of exposure to organic solvents like dichloromethane (DCM) and 1,2-dicholoropropane (1,2-DCP) used in the printing process. Patients presented with regional dilation of the bile ducts and high serum γ-glutamyl transpeptidase activity (Kubo et al. 2018). Studies have also shown that exposure to toxins like nitrosamines and other chemicals used in the rubber and dye industries (including tetramethyl thiuram disulfide and zinc-diethyldithiocarbamate) have been implicated in the development of GBC and CCA (Gobbi et al. 2020).

Lifestyle

Diabetes, obesity, smoking, and alcohol consumption are increasingly recognized as risk factors for BTCs, however with some controversy as studies on their effects have been inconclusive (Baidoun et al. 2022; Makiuchi et al. 2019; McGee et al. 2019). Different studies have reported a positive association between type II diabetes and iCCA as well as eCCA (Khan et al. 2019). It has been difficult to assess the specific contribution of each factor with BTC, for example, among diabetes, obesity, and gallstones, due to their strong intrinsic association. Whether the potential association between diabetes and CCA may be direct or mediated by other risk factors, such as obesity, chronic liver disease, or non-alcoholic fatty liver disease (NAFLD), remains unclear.

Alcohol

Heavy drinkers (average alcohol consumption ≥ 50 grams alcohol/day) have a marked increased risk of BTCs, as well as cases of alcoholic cirrhosis, because they cause scarring, long-lasting irritation of the biliary tissue, as well as formation of gallstones (Kirstein and Vogel 2016; Makiuchi et al. 2019). Alcohol consumption was only associated with iCCA. In a study performed by McGee et al. ever, former, and current smoking were associated with an increased risk for eCCA and ampulla of Vater (e.g. current vs never smokers HR = 1.69, 95% CI = 1.34 to 2.13 and 2.22, 95% CI = 1.69 to 2.92, respectively) (McGee et al. 2019). Current smoking and smoking intensity were also associated with iCCA (>40 cigarettes per day vs never smokers HR = 2.15, 95% CI = 1.15 to 4.00). The association between smoking and GBC was not determinant. There was high heterogeneity among the studies performed to study the causal role of smoking and alcohol abuse in determining the risk of BTC. Findings highlight the elevated heterogeneity across BTCs and further studies are warranted.

Obesity

As observed for other GI malignancies, there is a positive association between high body mass index (BMI; Obese BMI ≥ 30 kg/m^2) and elevated risk for BTCs, but the exact mechanism still needs to be elucidated (Osataphan et al. 2021). Thus, the role of obesity on BTCs remains controversial, particularly for CCA. It seems to be a link with changes in microbiome composition, lipid levels, blood sugar, poor diet (e.g. elevated red and processed meat intake, raw fish, low intake of fruits and vegetables), or inflammation (Wang et al. 2022). As for all cancers, there is a correlation among age and BTCs. Although BTCs are common in older age-groups, CCA risk increases after the age of 45 and for GBC, age-specific incidence rates rise steeply from age 50. However, the average is over the age of 65. Patients aged ≥75 years had 5–10 times higher mortality rates than the overall BTC rate in all countries.

Prevention

Prevention is pivotal in endemic regions for parasites and HBV. Prevention of liver fluke infection includes health education regarding food handling, cooking procedures, and consumption. For example, in northeast Thailand, the Lawa model (a liver fluke control program), has been implemented to modify food (raw fish) consumption (Brindley et al. 2021). It includes reduction in raw fish consumption (which are part of the traditional culture), vaccination, antiviral therapies, as well as avoiding exposure to toxins and hazardous chemicals, or minimizing smoking and alcohol consumption (Brindley et al. 2021).

Screening and Surveillance

Around 20–25% of iCCA are diagnosed incidentally (i.e. during surveillance of cirrhotic livers) (Alvaro et al. 2011). eCCAs (distal or perihilar) on the other hand, remain undetectable until advanced stages where biliary obstruction manifests as jaundice – the most common form of presentation of this tumor type. GBCs are often found incidentally following surgical removal of the gallbladder (García et al. 2020).

Surveillance is the optimal way in which clinicians are able to identify any early signs of disease, including cancer, through the means of repeated applications of investigations (blood analysis, biomarker analysis, imaging etc.) in order to limit patient mortality and to increase and improve patient survival and outcome respectively (Vithayathil and Khan 2022). However, principles for implementation of screening programs require the condition to pose an important health issue with high morbidity and mortality rates, adequate understanding of its pathophysiology (development and course), a latency period, and early symptoms which offer a window of opportunity for detection as well as substantial clinical benefit to those diagnosed early. Moreover, target (at high-risk) cohorts should be clearly defined, sufficiently accurate, and acceptable tests which are cost effective for healthcare systems compared to the expenditure incurred as part of its management, should be available (Shieh et al. 2016). With respect to BTCs, these requirements remain largely unmet. Considering a higher incidence in certain populations and their association with certain conditions (PSC), identification of risk factors and cohorts in which screening could potentially be performed is pivotal (Muñoz-Martínez et al. 2022).

High-risk groups include patients with primary sclerosing cholangitis (PSC), who have a 40 fold risk for HPB malignancies, an annual incidence of CCA estimated at 0.5–1.5%, and a reported lifetime incidence of 20% (Card et al. 2008; Patel 2011).

Other large high-risk groups include patients who are from endemic regions with liver flukes infestations (*O. viverrini* and *C. sinensis*), and/or the consumption of under-cooked cyprinoid fish consumption, patients with recurrent cholangitis or cholecystitis, and patients with significant occupational risk factors (rubber and dyes industry, and agriculture and pesticide use) (Brindley et al. 2021).

Patients with Occupational Risk

For screening and surveillance in patients with occupational hazards for the development of biliary tract cancers, a study determined that routine health checks with a number of blood analysis including serum γ-glutamyl transpeptidase (γ-GT), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), carbohydrate antigen 19–9 (CA 19–9), and carcinoembryonic antigen (CEA) levels in tandem with abdominal ultrasonography (USS) were beneficial for this screening and surveillance process (Sombattheera et al. 2015). In the presence and/or at the time of diagnosis of a biliary tract malignancy, these serum factors increase. The abdominal ultrasonography prior to confirmatory diagnosis often depicts regions of biliary duct dilatation in the region of suspected malignancy. This regional biliary duct dilatation is often due to tumor-induced stenosis, parenchymal space-occupying lesions, and/or an associated lymph node swelling causing regional duct occlusion and proximal and/or distal biliary duct dilatation (Kubo et al. 2016).

Liver Fluke Endemic Regions

Endemic regions including northern Thailand and South-East Asia have implemented large-scale screening and surveillance for liver fluke infection and also biliary tract cancers. They have introduced extensive testing of stool and blood samples, specifically investigating for fluke ova serological assay respectively, attempting to the diagnosis of Opisthorchiasis and Clonorchiasis infections (Siripongsakun et al. 2018). Screening initiatives in this region have also coupled these tests with abdominal ultrasonography (USS) with follow up imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) upon any preliminary positive findings from surveillance, although USS surveillance has shown to have positive benefits in areas highly endemic for CCA by reducing CCA patient mortality, due to high surveillance pick up-rate of premalignant lesions and early-stage diseases (Olthof et al. 2016). A five-year population-based study by Sungkasubun et al. implemented a six-monthly screening program comprised of blood testing, stool examination, and serial abdominal USS. The study enrolled 4,255 eligible individuals within the first three years of the study and BTCs were detected in 32 patients (mean age of 51.9 years (41–62 years)). There were 21 out of 32 cases of BTCs, which were detected at a curative resectable stage. The 1- and 2-year overall survival rates of CCA patients were 90.9% and 61.5%, respectively. The screening programmed improved prognosis in these resectable cases with 100% survival at 1-year and 77.8% survival at 2-years. This highlights the fact that the surveillance and detection of premalignant BTC lesions and/or early-stage resectable CCA by USS resulted in improved clinical outcomes (Sungkasubun et al. 2016).

Primary Sclerosing Cholangitis

Primary Sclerosing Cholangitis (PSC) is recognized as one of the most important risk factors for CCA development, with an increased lifetime incidence of 20% and ~ 500 fold increase in the relative risk for developing CCA compared to the general population. A high proportion (up to 50%) of CCA patients have concomitant PSC (Rabiee and Silveira 2021). As described prior, PSC tends to pre-dominantly affect the distal bile ducts and also intrahepatic ducts, which is where we primarily see biliary tract lesions, including CCA. With the increased risk driving CCA development, it is imperative to establish appropriate surveillance strategies in asymptomatic PSC patient cohorts (Fung et al. 2019). The combination of serological assays and non-invasive surveillance imaging including CT, USS, and/or MRCP (magnetic resonance imaging cholangiopancreatography) imaging techniques. MRI is often deemed a superior modality compared to USS for surveillance and the detection of early-stage perihilar CCA in patients with PSC (Satiya et al. 2020). Upon high suspicion of malignancy, confirmatory diagnosis often requires invasive endoscopic procedures (cholangioscopy) with or without tissue sampling (biopsy), or conventional cytology, or fluorescence in situ hybridization (FISH) analysis (Figure 3). However in the event of low pre-test probability for CCA (i.e. low to normal CA 19–9 levels, absent jaundice, and no recorded weight loss) these techniques and resultant biopsies can lack sensitivity and provide indeterminate histopathological results (Rizvi et al. 2018).

Biomarkers

Diagnosis of biliary tract cancers relies on a combination of clinical findings, imaging (ultrasonography, computerized tomography, and magnetic resonance imaging), and serum biomarkers (Macias et al. 2018, 2019). Confirmation by histopathology or cytology is often required, as the combination of different techniques increases individual test diagnostic performances. While the diagnostic workup and management are reviewed in Chapter 20 here we will discuss clinically applied and novel biomarkers described in the diagnosis of BTCs.

Serum Biomarkers

Circulating biomarkers used in clinic to diagnose biliary tract cancers are carbohydrate antigen 19–9 (CA19-9), carcinoembryonic antigen (CEA) and, in some cases, carbohydrate antigen 125 (CA125). Despite their wide application, their diagnostic accuracy remains suboptimal, and they are mostly used for confirmation of diagnosis, monitoring of disease and prediction of risk of tumor relapse (Banales et al. 2016; Srivastava and Creek 2019).

CA19-9

CA19-9 (also known as Lewis Antigen A) is a sialylated tetrasaccharide found on the surface of cells. Under normal conditions, CA19-9 plays a role in cellular recognition, but it is also found over-expressed in cancers of the biliary tract. CA19-9 is the primary serological biomarker used in CCA and GBC diagnosis, with levels higher than 100 U/mL indicating the presence

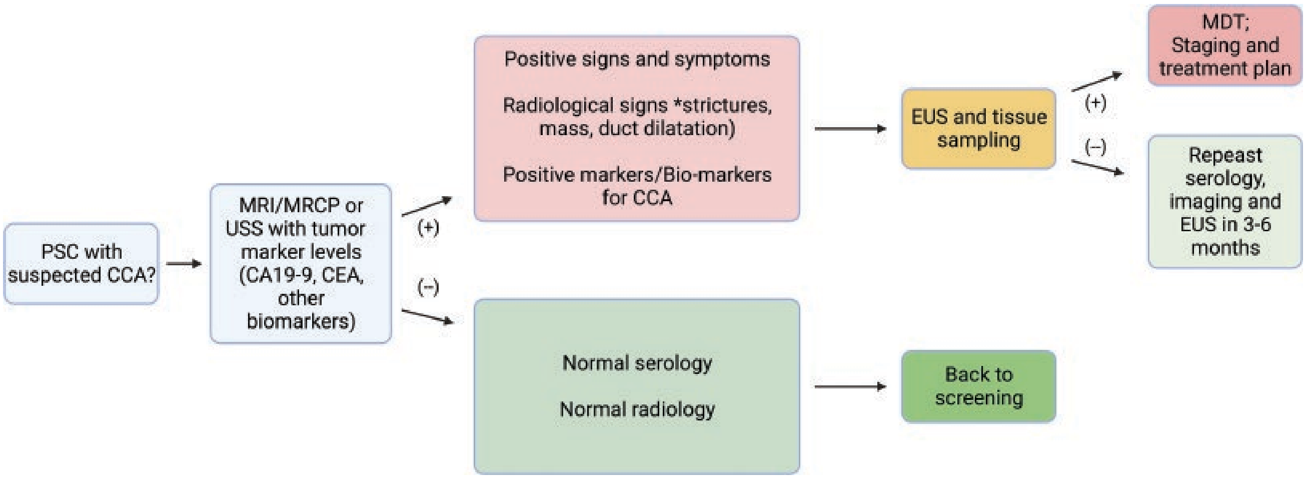
PSC with suspected CCA?
MRI/MRCP or USS with tumor marker levels (CA19-9, CEA, other biomarkers)
(+)
(–)
Positive signs and symptoms
Radiological signs *strictures, mass, duct dilatation)
Positive markers/Bio-markers for CCA
EUS and tissue sampling
(+)
(–)
MDT; Staging and treatment plan
Repeast serology, imaging and EUS in 3-6 months
Normal serology
Normal radiology
Back to screening

Figure 3 Cholangiocarcinoma surveillance algorithm is patients with Primary Sclerosing Cholangitis (PSC). MRI – Magnetic Resonance Imaging; MRCP – Magnetic Resonance Cholangio-pancreatography; USS – Ultrasound Scan; EUS – Endoscopic Ultrasound; MDT – Multi-disciplinary Team.

of malignancy (Patel et al. 2000). The sensitivity and specificity of this marker for the detection of CCA varies among studies and groups of comparison, ranging between 50–80% and 40–70%, respectively, with increasing performance in late-stage tumors (Khan et al. 2012). A study led by Levy showed that the sensitivity and specificity of CA19-9 in a subgroup of CCA patients with a background of PSC increased to 79 and 98% for CCA diagnosis (Levy et al. 2005). Regarding GBC, the diagnostic accuracy of CA19-9 has not yet been validated (Li et al. 2019). Wang et al. reported a sensitivity and specificity of 71.7% and 96.1% in differentiation of GBC patients from those with benign disease and healthy individuals (Wang et al. 2014). In a more recent study, CA19-9 has been proposed as a predictor of resectability in GBC at a cut-off of 98.91 U/mL for R0 resection (76.3% sensitivity and 70.8% specificity) (Liu et al. 2019).

One of the reasons for its limited diagnostic value is that levels of CA19-9 are also raised in cases of benign biliary obstruction (i.e., jaundice) and in patients with pancreatic cancer. Furthermore, it is important to take into consideration during study design, and accuracy estimation, that around 7% of the general population do not express one of the main precursors of CA19-9, the fucosyltransferase 3 (FUT3) (Rahnemai-Azar et al. 2017). Lewis (A) negative patients do not show any increase in the serum levels of CA19-9 even in the presence of histologically confirmed cancer.

Carcino-Embryonic Antigen A (CEA)

CEA, a cell-surface anchored cell adhesion glycoprotein was first described as a marker of colorectal cancer. CEA is found to be elevated in serum (CEA > 5 ng/mL) of around 30% of patients with biliary tract cancer (Fang et al. 2019). CEA is highly expressed during fetal development but its levels in adults are reduced to typically between 2–4 ng/mL. An increase in CEA may also indicate presence of other cancers like pancreatic or bowel cancer; or even some benign conditions such as inflammatory bowel disease, cholangitis, hepatitis, or cirrhosis (Rule et al. 1973).

Carbohydrate Antigen 125 (CA125)

CA125, also known as mucin (MUC) 16, is a glycoprotein found in the epithelium of ovaries, cornea, and the respiratory tract. First described as a biomarker of ovarian cancer, CA125 overexpression has also been linked to other types of cancers including CCA (as well as pancreatic cancer). Although around 65% of patients with CCA express higher than normal levels of CA125 (cut-off value of 37 U/mL), similarly to CEA, CA125 a non-specific marker of BTCs as it is overexpressed by multiple cancers (Felder et al. 2014). Abnormal serum levels of this marker are observed in ovarian, breast, colorectal, pancreatic, or lung cancers, and in some cases of cirrhosis (Moss et al. 2005).

Histological Biomarkers of BTCs

Histological diagnosis of BTCs involve immunohistochemistry for specific markers as part of confirmation of site of tumor origin. Cytokeratins (CK) 7 and 19 are epithelial structural proteins that are used in CCA diagnosis. CK7 and CK9 however, are non-specific markers as they are also expressed by other adenocarcinomas as well as by HCCs (Takahashi et al. 2021; Yang et al. 2021).

One of the main challenges in the diagnosis of iCCAs is their differentiation from poorly differentiated HCC. Applying a combination of histological markers including hepatocyte paraffin 1 (HepPar-1), arginase-1 (Arg1), CD10, alpha-fetoprotein (AFP), and CEA is useful. In some cases, the expression pattern of glutamine synthetase (GS), glypican 3 (GPC3), or heat shock protein 70 (HSP70), are also informative. The epithelial cell adhesion molecule (EpCAM) was also considered for the differentiation of HCC from iCCA but it also shows expression in some poorly differentiated HCC and other carcinomas, limiting its diagnostic potential (Proca et al. 2000).

The current diagnosis of GBC is based on CK7 positive staining. Additionally, immunohistochemistry of HepPar-1 and AFP can be performed in rare cases of hepatoid adenocarcinoma variant of GBC. Moreover, claudins, which are transmembrane proteins present in the tight junctions between epithelial cells, have been proposed for the differential diagnosis of iCCA/eCCA and GBC, although their expression pattern can be similar to PDAC, compromising its specificity (Lodi et al. 2006).

Mucins, a group of highly glycosylated proteins secreted by epithelial cells, can be analyzed during routine histological staining of resected tumors, as they have been linked with prognosis (Kasprzak and Adamek 2019). iCCA with high-mucin content show shorter survival rates than low-mucin content (Chi et al. 2018; Komuta et al. 2012). Similarly, Lu et al. found that pCCAs with high mucin expression are indicative of worse prognosis compared to low mucin expressing tumors (Lu et al. 2019).

Emerging Biomarkers

The limited diagnostic accuracy of the circulating biomarkers currently used in clinic (i.e. CA19-9, CEA, CA125) motivates the search for novel non-invasive biomolecules with improved sensitivity and specificity for BTCs. An evolving multi-omics era (genomics, transcriptomics, proteomics, epigenomics, and metabolomics), enabled the discovery of biomolecules which can be obtained using minimally invasive techniques from a variety of body fluids including serum, plasma, bile, or urine. Although numerous reports of novel biomarkers have emerged in recent years (Figure 4), a detailed review of the field is beyond the scope of this chapter. Here we will discuss a few key diagnostic and prognostic biomarkers for detection and prognosis of BTCs. Variations in circulating levels of nucleic acids, proteins, metabolites, or even whole cells which are diagnostic and/or prognostic in the context of BTCs, are increasingly described.

Targeted next-generation sequencing (NGS) identifies mutations in CCA biopsies, enabling characterization of BTCs and highlight potential therapeutic targets (Qin 2019). Studies have shown these assays have been able to even decipher biological causative links from the biopsies being tested (Lu and Zhan 2018). One study has described a profile of genes (7 overexpressed and 3 under expressed) in patients with Opisthorchis viverrini-related CCA (Subrungruanga et al. 2013).

Circulating Tumor DNA (CtDNA)

ctDNA are small fragments of DNA (typically between 150–200 base pairs) that are released into the bloodstream when cancer cells undergo cell death (Chakrabarti et al. 2020). The presence of ctDNA can also been detected in bile (Shen et al. 2019). They have proven to be of extraordinary value as they are reflective of tumor size, aggressiveness, and of the mutational landscapes of primary tumors. The identification of commonly mutated genes in BTC (i.e. KRAS, NRAS, BRAF, and PIK3CA) is possible through their isolation and genomic analysis (Andersen and Jakobsen 2016). ctDNA sampling can be of potential interest in the diagnosis of BTCs, where adequate sampling of tissue from a heterogeneous tumor can be challenging.

MicroRNAs (miRs)

Cell-free RNAs of small size or microRNAs (miRs) are also abundant in body fluids (blood, bile, and urine). miRNAs act to repress the target mRNA and as a result, are an important biomarker for diagnostic and prognostic purposes (Condrat et al. 2020). Studies have highlighted around 70 miRNAs that can affect the genetic expression of genes that mediate signaling pathways involving cell proliferation, cell exhaustion, cell senescence, angiogenesis, evasion of the immune response, dissemination, and metastases (Rajasegaran et al. 2021). miRNAs can be attained from liquid and solid biopsies and are relatively easy to acquire and meta-analyses concluded that miRNAs have a high diagnostic accuracy (Sun et al. 2018). miRs are resistant to degradation and they can easily be detected by RT-PCR at a low cost (Afonso et al. 2016). In two large meta-analysis, the diagnostic potential of miRs for biliary tract cancer detection was evaluated, reporting the highest performance in bile (AUC = 0.950) (Liang et al. 2016; Zhou et al. 2017). Serum miRs reached an AUC of 0.913 and urine miRs of 0.745, highlighting the strong diagnostic potential of these biomolecules (Liang et al. 2016; Zhou et al. 2017).

There are a few miRNAs that are used in assessing patients with suspected BTCs. miRNA-21 is an oncogenic miRNA that is upregulated in a significant subset of cholangiocarcinoma and is an accurate diagnostic biomarker (area under the curve (AUC) of 0.89) (Wang et al. 2015). Wang et al. reported that serum levels of miR-21 differentiated iCCA patients (n = 74) from healthy controls (n = 74) with test performance (AUC) of 0.908 (Wang et al. 2015). Similarly, Correa-Gallego and collaborators reported an AUC of 0.940 for miR-21 (Correa-Gallego et al. 2016). Silakit reported that the combined levels of miR-21 and miR-192 in urine differentiated CCA patients from healthy controls (AUC of 0.849) (Silakit et al. 2017).

miR-412, miR-640, miR-1537, and miR-3189 had a high accuracy to detect PSC-related CCA PSC disease and clinicians' use of miRNA described above, in conjunction with CA19-9 can lead to an accurate CCA diagnosis (Voigtländer et al. 2015). Although promising, validation studies combining

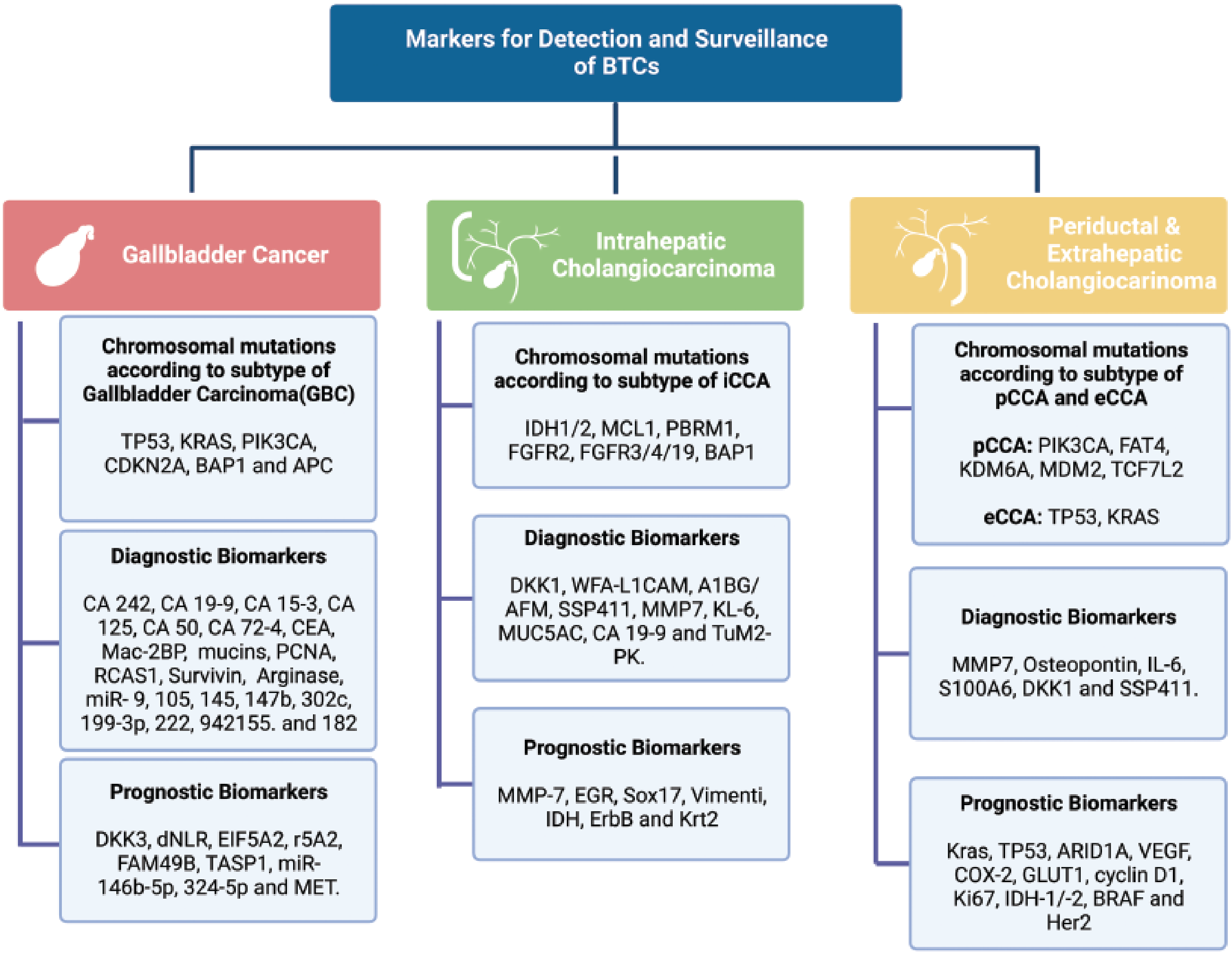
Markers for Detection and Surveillance of BTCs
Gallbladder Cancer
Intrahepatic Cholangiocarcinoma
Periductal & Extrahepatic Cholangiocarinoma
Chromosomal mutations according to subtype of Gallbladder Carcinoma(GBC)
TP53, KRAS, PIK3CA, CDKN2A, BAP1 and APC
Diagnostic Biomarkers
CA 242, CA 19-9, CA 15-3, CA 125, CA 50, CA 72-4, CEA, Mac-2BP, mucins, PCNA, RCAS1, Survivin, Arginase, miR- 9, 105, 145, 147b, 302c, 199-3p, 222, 942155. and 182
Prognostic Biomarkers
DKK3, dNLR, EIF5A2, r5A2, FAM49B, TASP1, miR-146b-5p, 324-5p and MET.
Chromosomal mutations according to subtype of iCCA
IDH1/2, MCL1, PBRM1, FGFR2, FGFR3/4/19, BAP1
Diagnostic Biomarkers
DKK1, WFA-L1CAM, A1BG/AFM, SSP411, MMP7, KL-6, MUC5AC, CA 19-9 and TuM2-PK.
Prognostic Biomarkers
MMP-7, EGR, Sox17, Vimenti, IDH, ErbB and Krt2
Chromosomal mutations according to subtype of pCCA and eCCA
pCCA: PIK3CA, FAT4, KDM6A, MDM2, TCF7L2
eCCA: TP53, KRAS
Diagnostic Biomarkers
MMP7, Osteopontin, IL-6, S100A6, DKK1 and SSP411.
Prognostic Biomarkers
Kras, TP53, ARID1A, VEGF, COX-2, GLUT1, cyclin D1, Ki67, IDH-1/-2, BRAF and Her2

Figure 4 Evolving biomarkers for detection, prognostication, and surveillance of Biliary Tract Cancers (BTCs). An evolving multi-omics era (genomics, transcriptomics, proteomics, epigenomics, and metabolomics), enabled the discovery of biomolecules which can be obtained using minimally invasive techniques (Lang et al. 2021; Lin et al. 2021; Macias et al. 2019; Rahnemai-Azar et al. 2017).

information of large cohort of patients from different geographic locations are still needed before these markers can be translated into the clinical practice.

Proteins

Proteomic studies have identified some circulating proteins with, potentially, better diagnostic value for BTCs than the ones currently used in clinic. CYFRA 21–1, a soluble fragment of CK19 was also found elevated in the serum of BTC patients (n = 134) compared to benign biliary disease (n = 52), generating an AUC of 0.851 (Huang et al. 2015). The matrix metalloproteinase-7 (MMP7), an enzyme with a role of degradation of components of the extracellular matrix, is also upregulated in the blood of patients with CCA compared with benign biliary disease (AUC = 0.840) (Leelawat et al. 2010). Similarly, osteopontin (OPN), a structural protein typically found in bone tissue, has been proposed as a marker of CCA, being elevated in the serum of a cohort of 80 cancer cases compared to healthy individuals (AUC = 0.964) (Loosen et al. 2017). The pro-inflammatory cytokine interleukin 6 (IL-6), was found elevated in BTC cases versus healthy (AUC = 0.875), and making it a promising marker for further analysis (Cheon et al. 2007). CA242 (a sialylated carbohydrate antigen) showed great specificity for GBC (98.7%), performing better than CA19–9 and CEA alone. The combination of this marker with CA19–9 and CA125 reached a specificity of 100%, although it did not improve its sensitivity (Rana et al. 2012).

Extracellular Vesicles (EVs)

EVs are heterogeneous lipid bilayer spheres released by cells as part of inter-cellular communication processes. Within their core, DNA, RNA, proteins, or metabolites are carried as cargo.

EVs can be found in blood, bile, saliva, urine, and ascitic fluid, and the number of EVs, cargo, and surface markers can correlate with the cell of origin, highlighting their potential for cancer detection (Lapitz et al. 2018). Arbelaiz and co-workers analyzed the protein content of EVs isolated from the serum of CCA patients (n = 43) (Arbelaiz et al. 2017). They found increased levels of aminopeptidase N (AMPN), pantetheinase (VNN1) and polymeric immunoglobulin receptor (PIGR) compared to healthy controls (n = 32), with AUC ranging from 0.844 to 0.878. When they compared CCA with PSC cases (n = 30), the proteins with best performance were fibrinogen gamma chain (FIBG, AUC = 0.796), alpha-1-acid glycoprotein (A1AG1, AUC = 0.794) and protein S100A8 (AUC = 0.759).

A different study by Lapitz et al. looking into the RNA content in serum EVs found a panel of 3 RNAs (i.e. CMIP, NME1, CKS1B) with the best performance (AUC = 1.00) when comparing CCA patients with a control group formed by patients with PSC, UC, and healthy individuals (Lapitz et al. 2020). The same group also reported that in urine, the combination of two RNAs (UBE2C and SERPINB1) were able to achieve an AUC of 0.812. However, the small nuclear RNA RNU11 was the biomarker with single best performance in urine EVs of the study (AUC = 0.830). Lastly, Li and collaborators described a panel of miRs present in bile EVs of CCA (n = 46) patients compared to individuals with benign biliary diseases (n = 50) (Li et al. 2014). The panel formed by miR-191, -486-3p, -1274b, -16, and -484 was able to differentiate the two groups with a specificity and sensitivity of 96% and 67% respectively.

Circulating Tumor Cells (CTCs)

Circulating tumor cells are cancer cells released to the bloodstream. They can be found at low concentrations in the blood of cancer patients (> 10 cells/mL) and have recently been studied for the detection of biliary tract cancers. In a large study by Yang et al., CTCs were found in 26% of patients with BTC using an enrichment platform based on the expression of EpCAM marker on their surface (Yang et al. 2016). They reported that CTCs correlated with prognosis especially in metastatic cases, and also with overall survival. Moreover, these cells can also be used to study the mutation pattern of the source tumor and be able to select therapies for personalized medicine.

Key Take Home Messages

- The low five-year survival rates associated with pancreatic and biliary tract cancers are explained by a most often non-specific clinical course and late-stage diagnosis.
- Early tumor detection is key for improved outcomes. Due to a low incidence and lifetime risk, and a relatively low performance of current diagnostics, screening for pancreatic cancer in the general population is not feasible.
- International protocols for screening and surveillance in high-risk patients with pre-malignant cysts, genetic predisposition, and new-onset diabetes are under development yet screening for pancreatic cancer is mostly done in research settings.
- Patients over 50 years of age and diabetes of less than 1-year duration have a high relative risk for pancreatic cancer. This cohort represents an attractive target for screening in primary care.
- High risk groups for BTCs include patients with primary sclerosing cholangitis and subjects exposed to occupational hazard or living in liver fluke (O. viverrini and C. sinensis) endemic areas. The diagnosis of pancreatic and biliary tract cancers requires a multi-modal approach including clinical findings, imaging and tumor marker levels yet the diagnostic performance of clinically applied tests (such as CA19-9) is lacking. Similarly to pancreatic cancer, CA19-9 is mostly used for confirmation of diagnosis, monitoring of disease progression, and recurrence.

Areas for Further Research

- Screening of High-Risk individuals is beneficial yet requires understanding of tumor biology, identification of target cohorts, and the development of accurate and minimally invasive tests.
- Owing to advances in omics technologies, novel biomarkers (proteins, miRs, circulating cell free DNA and tumor cells) and panels for detection and prognostication of tumors, are increasingly reported. These, however, will require large scale validations prior to clinical implementation.
- Guidance and protocols for prevention, screening, and surveillance in high-risk cohorts for BTC is evolving.

Trusted Websites for Further Reading

Suggested resources for early detection and screening in pancreatic and BTC:

- https://lctc.org.uk/affiliates/ukedi
- https://www.europactrial.com
- https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-blood-urine-tissue-samples-help-diagnose-pancreatric-cancer-neuroendocrine-tumour-pancreas-adepts
- http://www.enscca.org
- https://ammf.org.uk/cca-uk

References

Afonso, M.B., Rodrigues, P.M., Simão, A.L., and Castro, R.E. (2016). Circulating microRNAs as potential biomarkers in non-alcoholic fatty liver disease and hepatocellular carcinoma. *J Clin Med* 5 (3): 30.

Alberts, C.J., Clifford, G.M., Georges, D. et al. (2022 August). Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. *Lancet Gastroenterol Hepatol* 7 (8): 724–735.

Alvaro, D., Bragazzi, M.C., Benedetti, A. et al. (2011). Cholangiocarcinoma in Italy: a national survey on clinical characteristics, diagnostic modalities and treatment. Results from the “Cholangiocarcinoma” committee of the Italian association for the study of liver disease. *Dig Liver Dis* 43 (1): 60–65.

Amaral, A.F., Porta, M., Silverman, D.T. et al. (2012). Pancreatic cancer risk and levels of trace elements. *Gut* [Internet] 20111219th ed. 61 (11): 1583–1588. Available from https://www.ncbi.nlm.nih.gov/pubmed/22184070.

Andersen, R.F. and Jakobsen, A. (2016 July). Screening for circulating RAS/RAF mutations by multiplex digital PCR. *Clin Chim Acta* 458: 138–143.

Andrén-Sandberg, A. (2012 May). Diagnosis and management of gallbladder polyps. *N Am J Med Sci* 4 (5): 203–211.

Antwi, S.O., Eckert, E.C., Sabaque, C.V. et al. (2015). Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. *Cancer Causes Control* [Internet] 20150821st ed. 26 (11): 1583–1591. Available from https://www.ncbi.nlm.nih.gov/pubmed/26293241.

Arbelaiz, A., Azkargorta, M., Krawczyk, M. et al. (2017 October). Serum extracellular vesicles contain protein biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology* 66 (4): 1125–1143.

Aslanian, H.R., Lee, J.H., and Canto, M.I. (2020 July). AGA clinical practice update on pancreas cancer screening in high-risk individuals: expert review. *Gastroenterology* 159 (1): 358–362.

Athauda, A., Fong, C., Lau, D.K. et al. (2020 June). Broadening the therapeutic horizon of advanced biliary tract cancer through molecular characterisation. *Cancer Treat Rev* 86: 101998.

Aughton, K., Elander, N.O., Evans, A. et al. (2021 November 17). hENT1 predicts benefit from gemcitabine in pancreatic cancer but only with low CDA mRNA. *Cancers (Basel)* 13 (22): 5758.

Aune, D., Greenwood, D.C., Chan, D.S. et al. (2012). Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol* [Internet] 20110902nd ed. 23 (4): 843–852. Available from https://www.ncbi.nlm.nih.gov/pubmed/21890910.

Awuchi, C.G., Ondari, E.N., Nwozo, S. et al. (2022). Mycotoxins’ toxicological mechanisms involving humans, livestock and their associated health concerns: a review. *Toxins* 14.

Baidoun, F., Sarmini, M.T., Merjaneh, Z., and Moustafa, M.A. (2022 March 12). Controversial risk factors for cholangiocarcinoma. *Eur J Gastroenterol Hepatol* 34 (3): 338–344.

Bailey, P., Chang, D.K., Nones, K. et al. (2016 March 24). Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 531 (7592): 47–52.

Baison, G.N., Bonds, M.M., Helton, W.S., and Kozarek, R.A. (2019 July). Choledochal cysts: similarities and differences between Asian and Western countries. *World J Gastroenterol* 25 (26): 3334–3343.

Banales, J.M., Cardinale, V., Carpino, G. et al. (2016 May 20). Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European network for the study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 13 (5): 261–280.

Banales, J.M., Cardinale, V., Carpino, G. et al. (2016 May). Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European network for the study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 13 (5): 261–280.

Banales, J.M., Marin, J.J.G., Lamarca, A. et al. (2020 September 30). Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 17 (9): 557–588.

Baria, K., de Toni, E.N., Yu, B. et al. (2022). Worldwide incidence and mortality of biliary tract cancer. *Gastro Hep Advances* 1 (4): 618–626.

Barker, T., Fulde, G., Moulton, B. et al. (2020 December 5). An elevated neutrophil-to-lymphocyte ratio associates with weight loss and cachexia in cancer. *Sci Rep* 10 (1): 7535.

Bartsch, D.K., Gress, T.M., and Langer, P. (2012 August 5). Familial pancreatic cancer—current knowledge. *Nat Rev Gastroenterol Hepatol* 9 (8): 445–453.

Basisty, N., Kale, A., Jeon, O.H. et al. (2020 January 16). A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol* 18 (1): e3000599.

Bekaii-Saab, T.S., Bridgewater, J., and Normanno, N. (2021 September). Practical considerations in screening for genetic alterations in cholangiocarcinoma. *Ann Oncol* 32 (9): 1111–1126.

Bellin, M.D., Abu-El-Haija, M., Morgan, K. et al. (2018 April). A multicenter study of total pancreatectomy with islet autotransplantation (TPIAT): POST (Prospective Observational Study of TPIAT). *Pancreatology* 18 (3): 286–290.

Bellin, M.D., Freeman, M.L., Gelrud, A. et al. (2014 January). Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology* 14 (1): 27–35.

Ben, Q., Xu, M., Ning, X. et al. (2011). Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer* [Internet] 20110331st ed. 47 (13): 1928–1937. Available from https://www.ncbi.nlm.nih.gov/pubmed/21458985.

Benkerroum, N. (2020 February). Aflatoxins: producing-molds, structure, health issues and incidence in Southeast Asian and Sub-Saharan African Countries. *Int J Environ Res Public Health* 17 (4).

Bergquist, J.R., Puig, C.A., Shubert, C.R. et al. (2016 July). Carbohydrate Antigen 19-9 elevation in anatomically resectable, early stage pancreatic cancer is independently associated with decreased overall survival and an indication for neoadjuvant therapy: a national cancer database study. *J Am Coll Surg* 223 (1): 52–65.

Bridgewater, J., Galle, P.R., Khan, S.A. et al. (2014). Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 60 (6): 1268–1289.

Bridgewater, J.A., Goodman, K.A., Kalyan, A., and Mulcahy, M.F. (2016 May). Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling. *Am Soc Clin Oncol Educ Book* 36: e194–203.

Brindley, P.J., Bachini, M., Ilyas, S.I. et al. (2021 December 9). Cholangiocarcinoma. *Nat Rev Dis Primers* 7 (1): 65.

Brindley, P.J., Bachini, M., Ilyas, S.I. et al. (2021 September). Cholangiocarcinoma. *Nat Rev Dis Primers* 7 (1): 65.

Bryant, H.E., Schultz, N., Thomas, H.D. et al. (2005 April 14). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434 (7035): 913–917.

Buerlein, R.C.D. and Shami, V.M. (2021 January 23). Management of pancreatic cysts and guidelines: what the gastroenterologist needs to know. *Ther Adv Gastrointest Endosc* 14: 263177452110457.

Bujanda, L. and Herreros-Villanueva, M. (2017). Pancreatic cancer in Lynch Syndrome patients. *J Cancer* 8 (18): 3667–3674.

Cai, J., Chen, H., Lu, M. et al. (2021). Advances in the epidemiology of pancreatic cancer: trends, risk factors, screening, and prognosis. *Cancer Lett* [Internet] 20210630th ed. 520: 1–11. Available from https://www.ncbi.nlm.nih.gov/pubmed/34216688.

Calomino, N., Scheiterle, M.L.P.F., Fusario, D. et al. (2021). Porcelain gallbladder and its relationship to cancer. *Eur Surg- Acta Chir Austriaca* 53 (6): 311–316.

Canto, M.I., Harinck, F., Hruban, R.H. et al. (2013 March). International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 62 (3): 339–347.

Capello, M., Fahrmann, J.F., Rios Perez, M.v. et al. (2020 November). CES2 Expression in Pancreatic Adenocarcinoma is predictive of response to irinotecan and is associated with type 2 diabetes. *JCO Precis Oncol* 4: 426–436.

Capello, M., Lee, M., Wang, H. et al. (2015 August). Carboxylesterase 2 as a Determinant of response to Irinotecan and Neoadjuvant FOLFIRINOX therapy in pancreatic Ductal Adenocarcinoma. *JNCI: J Natl Cancer Inst* 107 (8).

Card, T.R., Solaymani-Dodaran, M., and West, J. (2008 June). Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. *J Hepatol* 48 (6): 939–944.

Cardinale, V., Bragazzi, M.C., Carpino, G. et al. (2018). Intrahepatic cholangiocarcinoma: review and update. *Hepatoma Res* 4 (6): 20.

Cardinale, V., Semeraro, R., Torrice, A. et al. (2010 November). Intra-hepatic and extra-hepatic cholangiocarcinoma: new insight into epidemiology and risk factors. *World J Gastrointest Oncol* 2 (11): 407–416.

Casadio, M., Biancaniello, F., Overi, D. et al. (2021 May). Molecular landscape and therapeutic strategies in cholangiocarcinoma: an integrated translational approach towards precision medicine. *Int J Mol Sci* 22 (11).

Cascetta, P., Cavaliere, A., Piro, G. et al. (2018). Pancreatic cancer and obesity: molecular mechanisms of cell transformation and chemoresistance. *Int J Mol Sci* [Internet] 20181025th ed. 19 (11): Available from https://www.ncbi.nlm.nih.gov/pubmed/30366466.

Chaiteerakij, R., Pan-Ngum, W., Poovorawan, K. et al. (2017 October). Characteristics and outcomes of cholangiocarcinoma by region in Thailand: a nationwide study. *World J Gastroenterol* 23 (39): 7160–7167.

Chakrabarti, S., Kamgar, M., and Mahipal, A. (2020). Targeted therapies in advanced biliary tract cancer: an evolving paradigm. *Cancers (Basel)* 12 (8): 2039.

Chari, S.T., Leibson, C.L., Rabe, K.G. et al. (2005). Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* [Internet] 129 (2): 504–511. Available from https://www.ncbi.nlm.nih.gov/pubmed/16083707.

Chari, S.T., Maitra, A., Matrisian, L.M. et al. (2022). Early Detection Initiative: a randomized controlled trial of algorithm-based screening in patients with new onset hyperglycemia and diabetes for early detection of pancreatic ductal adenocarcinoma. *Contemp Clin Trials* [Internet] 20211223rd ed. 113: 106659. Available from https://www.ncbi.nlm.nih.gov/pubmed/34954100.

Chen, M.J., Tsan, Y.T., Liou, J.M. et al. (2016). Statins and the risk of pancreatic cancer in Type 2 diabetic patients–A population-based cohort study. *Int J Cancer* [Internet] 20150831st ed. 138 (3): 594–603. Available from https://www.ncbi.nlm.nih.gov/pubmed/26296262.

Cheon, Y.K., Cho, Y.D., Moon, J.H. et al. (2007 October). Diagnostic utility of interleukin-6 (IL-6) for primary bile duct cancer and changes in serum IL-6 levels following photodynamic therapy. *Am J Gastroenterol* 102 (10): 2164–2170.

Cherif, S., Rais, H., Hakmaoui, A. et al. (2019). Linking Helicobacter pylori with gallbladder and biliary tract cancer in Moroccan population using clinical and pathological profiles. *Bioinformation* 15 (10): 735–743.

Chi, Z., Bhalla, A., Saeed, O. et al. (2018). Mucinous intrahepatic cholangiocarcinoma: a distinct variant. *Hum Pathol* 78: 131–137.

Chiorean, E.G., von Hoff, D.D., Reni, M. et al. (2016 April). CA19-9 decrease at 8 weeks as a predictor of overall survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. *Ann Oncol* 27 (4): 654–660.

Christakoudi, S., Pagoni, P., Ferrari, P. et al. (2021). Weight change in middle adulthood and risk of cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Int J Cancer* [Internet] 20201109th ed. 148 (7): 1637–1651. Available from https://www.ncbi.nlm.nih.gov/pubmed/33038275.

Clark, D.F., Maxwell, K.N., Powers, J. et al. (2019). Identification and confirmation of potentially actionable Germline mutations in Tumor-only genomic sequencing. *JCO Precis Oncol* 3.

Clements, O., Eliahoo, J., Kim, J.U. et al. (2020 January). Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *J Hepatol* 72 (1): 95–103.

Cohen, J.D., Li, L., Wang, Y. et al. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* (1979) [Internet] 20180118th ed. 359 (6378): 926–930. Available from https://www.ncbi.nlm.nih.gov/pubmed/29348365.

Cole, C.L., Beck, C.A., Robinson, D. et al. (2020 June 19). Dual energy X-ray Absorptiometry (DEXA) as a longitudinal outcome measure of cancer-related muscle wasting in mice. *PLoS One* 15 (6): e0230695.

Condrat, C.E., Thompson, D.C., Barbu, M.G. et al. (2020 January). miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis. *Cells* 9 (2).

Conroy, T., Hammel, P., Hebbar, M. et al. (2018 December 20). FOLFIRINOX or Gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 379 (25): 2395–2406.

Corral, J.E., Mareth, K.F., Riegert-Johnson, D.L. et al. (2019 January). Diagnostic yield from screening asymptomatic individuals at high risk for pancreatic cancer: a meta-analysis of Cohort studies. *Clin Gastroenterol Hepatol* 17 (1): 41–53.

Correa-Gallego, C., Maddalo, D., Doussot, A. et al. (2016). Circulating plasma levels of MicroRNA-21 and MicroRNA-221 are potential diagnostic markers for primary intrahepatic cholangiocarcinoma. *PLoS One* 11 (9): e0163699.

Dunlop, C.R., Wallez, Y., Johnson, T.I. et al. (2020 October 27). Complete loss of ATM function augments replication catastrophe induced by ATR inhibition and gemcitabine in pancreatic cancer models. *Br J Cancer* 123 (9): 1424–1436.

Elander, N.O., Aughton, K., Ghaneh, P. et al. (2018 April 9). Intratumoural expression of deoxycytidylate deaminase or ribonuceotide reductase subunit M1 expression are not related to survival in patients with resected pancreatic cancer given adjuvant chemotherapy. *Br J Cancer* 118 (8): 1084–1088.

Elander, N.O., Aughton, K., Ghaneh, P. et al. (2018 April 8). Expression of dihydropyrimidine dehydrogenase (DPD) and hENT1 predicts survival in pancreatic cancer. *Br J Cancer* 118 (7): 947–954.

Elta, G.H., Enestvedt, B.K., Sauer, B.G., and Lennon, A.M. (2018 April). ACG clinical guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol Suppl* 113 (4): 464–479.

Espinoza, J.A., Bizama, C., García, P. et al. (2016 April). The inflammatory inception of gallbladder cancer. *Biochim Biophys Acta* 1865 (2): 245–254.

The European Study Group on Cystic Tumours of the Pancreas. (2018). European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 67: 789–804.

Ewald, N., Kaufmann, C., Raspe, A. et al. (2012). Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev* [Internet] 28 (4): 338–342. Available from https://www.ncbi.nlm.nih.gov/pubmed/22121010.

Fahrner, R., Dennler, S.G., and Inderbitzin, D. (2020 August). Risk of malignancy in Caroli disease and syndrome: a systematic review. *World J Gastroenterol* 26 (31): 4718–4728.

Fang, T., Wang, H., Wang, Y. et al. (2019). Clinical significance of preoperative serum CEA, CA125, and CA19-9 levels in predicting the resectability of Cholangiocarcinoma. Shi Z, editor. *Dis Markers* 2019: 6016931.

Felder, M., Kapur, A., Gonzalez-Bosquet, J. et al. (2014 May 29). MUC16 (CA125): tumor biomarker to cancer therapy, a work in progress. *Mol Cancer* 13: 129.

Ferguson, S., Yang, K.S., Zelga, P. et al. (2022). Single-EV analysis (sEVA) of mutated proteins allows detection of stage 1 pancreatic cancer. *Sci Adv* [Internet] 20220422nd ed. 8 (16): eabm3453. Available from https://www.ncbi.nlm.nih.gov/pubmed/35452280.

Ferrone, C.R., Finkelstein, D.M., Thayer, S.P. et al. (2006 June 20). Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic Adenocarcinoma. *Clin Oncol* 24 (18): 2897–2902.

Ferrone, C.R., Levine, D.A., Tang, L.H. et al. (2009 January 20). *BRCA* Germline mutations in Jewish patients with pancreatic Adenocarcinoma. *Clin Oncol* 27 (3): 433–438.

Fiorini, C., Cordani, M., Padroni, C. et al. (2015 January). Mutant p53 stimulates chemoresistance of pancreatic adenocarcinoma cells to gemcitabine. *Biochim Biophys Acta Mol Cell Res BBA-Mol Cell Res* 1853 (1): 89–100.

Fragkou, N., Sideras, L., Panas, P. et al. (2021 July). Update on the association of hepatitis B with intrahepatic cholangiocarcinoma: is there new evidence? *World J Gastroenterol* 27 (27): 4252–4275.

Froeling, F., Casolino, R., Pea, A. et al. (2021 January 4). Molecular subtyping and precision medicine for pancreatic cancer. *J Clin Med* 10 (1): 149.

Fung, B.M., Lindor, K.D., and Tabibian, J.H. (2019 February). Cancer risk in primary sclerosing cholangitis: epidemiology, prevention, and surveillance strategies. *World J Gastroenterol* 25 (6): 659–671.

Ganesh, K., Stadler, Z.K., Cercek, A. et al. (2019 June 18). Immunotherapy in colorectal cancer: rationale, challenges and potential. *Nat Rev Gastroenterol Hepatol* 16 (6): 361–375.

García, P., Lamarca, A., Díaz, J. et al. (2020). Current and new biomarkers for early detection, prognostic stratification, and management of gallbladder cancer patients. *Cancers (Basel)* 12 (12): 3670.

Geoffroy-Perez, B., Janin, N., Ossian, K. et al. (2001 July 15). Cancer risk in heterozygotes for ataxia-telangiectasia. *Int J Cancer* 93 (2): 288–293.

Ghaneh, P., Wong, W.L., Titman, A. et al. (2016 May 20). PET-PANC: multi-centre prospective diagnostic accuracy and clinical value trial of FDG PET/CT in the diagnosis and management of suspected pancreatic cancer. *Clin Oncol* 34 (15_suppl): 4008–4008.

Gobbi, V.G., da Silva, T.G., Cunha, M.S. et al. (2020 September 5). Comparative study among TMTD, TBzTD, and ZBEC accelerators in isobutylene-isoprene elastomer vulcanization. *J Appl Polym Sci* 137 (33): 48965.

Goggins, M., Overbeek, K.A., Brand, R. et al. (2020 January). Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International cancer of the pancreas screening (CAPS) consortium. *Gut* 69 (1): 7–17.

Golan, T., Hammel, P., Reni, M. et al. (2019 July 25). Maintenance Olaparib for Germline *BRCA* -Mutated metastatic pancreatic cancer. *N Engl J Med* 381 (4): 317–327.

Greenhalf, W., Ghaneh, P., Neoptolemos, J.P. et al. (2014 January). Pancreatic cancer hENT1 expression and survival from Gemcitabine in patients from the ESPAC-3 trial. *JNCI: J Natl Cancer Inst* 106 (1).

Greenhalf, W., Lévy, P., Gress, T. et al. (2020 July). International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan pancreas society, and European pancreatic club. *Pancreatology* 20 (5): 910–918.

Griffin, J.F., Page, A.J., Samaha, G.J. et al. (2017 May). Patients with a resected pancreatic mucinous cystic neoplasm have a better prognosis than patients with an intraductal papillary mucinous neoplasm: a large single institution series.*Pancreatology* 17 (3): 490–496.

Gunn, J.S., Marshall, J.M., Baker, S. et al. (2014 November). Salmonella chronic carriage: epidemiology, diagnosis, and gallbladder persistence. *Trends Microbiol* 22 (11): 648–655.

Guo, X., Hu, Z., Rong, S. et al. (2022). Integrative analysis of metabolome and gut microbiota in patients with pancreatic ductal adenocarcinoma. *J Cancer* 13 (5): 1555–1564.

Hartwig, W., Hackert, T., Hinz, U. et al. (2011 August). Pancreatic cancer surgery in the new millennium. *Ann Surg* 254 (2): 311–319.

Heussner, A.H. and Bingle, L.E.H. (2015 October). Comparative Ochratoxin Toxicity: a review of the available data. *Toxins (Basel)* 7 (10): 4253–4282.

Hidalgo, M. (2010 April 29). Pancreatic cancer. *N Engl J Med* 362 (17): 1605–1617.

Hong, D.S., Fakih, M.G., Strickler, J.H. et al. (2020 September 24). KRAS ^{G12C} inhibition with Sotorasib in advanced solid tumors. *N Engl J Med* 383 (13): 1207–1217.

Hsing, A.W., Gao, Y.T., Han, T.Q. et al. (2007). Gallstones and the risk of biliary tract cancer: a population-based study in China. *Br J Cancer* 97 (11): 1577–1582.

Hu, C., Hart, S.N., Polley, E.C. et al. (2018 June). Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA* 319 (23): 2401–2409.

Hu, Z.I. and Lim, K.H. (2022 February). Evolving paradigms in the systemic treatment of advanced gallbladder cancer: updates in year 2022. *Cancers (Basel)* 14 (5).

Huang, L., Chen, W., Liang, P. et al. (2015 May). Serum CYFRA 21-1 in biliary tract cancers: a reliable biomarker for gallbladder carcinoma and intrahepatic cholangiocarcinoma. *Dig Dis Sci* 60 (5): 1273–1283.

Humphris, J.L., Chang, D.K., Johns, A.L. et al. (2012 July). The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol* 23 (7): 1713–1722.

Hundal, R. and Shaffer, E.A. (2014). Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 6: 99–109.

Ito, N., Tsujimoto, H., Ueno, H. et al. (2020). Helicobacter pylori-mediated immunity and signaling transduction in gastric cancer. *J Clin Med* 9.

Izquierdo-Sanchez, L., Lamarca, A., La Casta, A. et al. (2022 May). Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA registry. *J Hepatol* 76 (5): 1109–1121.

Jabłońska, B. (2012). Biliary cysts: etiology, diagnosis and management. *World J Gastroenterol* 18: 4801–4810.

Jackson, S.S., Van Dyke, A.L., Zhu, B. et al. (2019 August). Anthropometric risk factors for cancers of the biliary tract in the biliary tract cancers pooling project. *Cancer Res* 79 (15): 3973–3982.

Jarnagin, W.R. and Winston, C. (2005). Hilar cholangiocarcinoma: diagnosis and staging. *Hpb* 7 (4): 244–251.

Ji, B.T., Silverman, D.T., Stewart, P.A. et al. (2001). Occupational exposure to pesticides and pancreatic cancer. *Am J Ind Med* [Internet]. 39 (1): 92–99. Available from https://www.ncbi.nlm.nih.gov/pubmed/11148019.

Johnston, C.D. and Bullman, S. (2022). The tumour-associated microbiome. *Nat Rev Gastroenterol Hepatol* [Internet]. 19 (6): 347–348. Available from https://www.ncbi.nlm.nih.gov/pubmed/35361914.

Kalbi, D.P., Bapatla, A., Chaudhary, A.J. et al. (2021 July). Surveillance of Gallbladder polyps: a literature review. *Cureus* 13 (7): e16113.

Kamisawa, T., Kuruma, S., Chiba, K. et al. (2017 February). Biliary carcinogenesis in pancreaticobiliary malfunction. *J Gastroenterol* 52 (2): 158–163.

Kamisawa, T., Wood, L.D., Itoi, T., and Takaori, K. (2016 July). Pancreatic cancer. *Lancet* 388 (10039): 73–85.

Kartal, E., Schmidt, T.S.B., Molina-Montes, E. et al. (2022). A faecal microbiota signature with high specificity for pancreatic cancer. *Gut* [Internet] 20220308th ed. 71 (7): 1359–1372. Available from https://www.ncbi.nlm.nih.gov/pubmed/35260444.

Kasprzak, A. and Adamek, A. (2019). Mucins: the old, the new and the promising factors in hepatobiliary carcinogenesis. *Int J Mol Sci* 20 (6): 1288.

Khalaf, N., Yuan, C., Hamada, T. et al. (2018). Regular use of aspirin or non-aspirin nonsteroidal anti-inflammatory drugs is not associated with risk of incident pancreatic cancer in two large cohort studies. *Gastroenterology* [Internet] 20171208th ed. 154 (5): 1380–1390.e5. Available from https://www.ncbi.nlm.nih.gov/pubmed/29229401.

Khan, S.A., Davidson, B.R., Goldin, R.D. et al. (2012 December). Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 61 (12): 1657–1669.

Khan, S.A., Tavolari, S., and Brandi, G. (2019 May 24). Cholangiocarcinoma: epidemiology and risk factors. *Liver International* 39 (S1): 19–31.

Kim, H.J., Kim, J.S., Joo, M.K. et al. (2015 December). Hepatolithiasis and intrahepatic cholangiocarcinoma: a review. *World J Gastroenterol* 21 (48): 13418–13431.

Kirstein, M.M. and Vogel, A. (2016). Epidemiology and risk factors of Cholangiocarcinoma. *Visc Med* 32 (6): 395–400.

Klein, E.A., Richards, D., Cohn, A. et al. (2021). Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol* [Internet] 20210624th ed. 32 (9): 1167–1177. Available from https://www.ncbi.nlm.nih.gov/pubmed/34176681.

Ko, A.H., Hwang, J., Venook, A.P. et al. (2005 July 5). Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. *Br J Cancer* 93 (2): 195–199.

Kohi, S., Macgregor-Das, A., Dbouk, M. et al. (2022). Alterations in the duodenal fluid microbiome of patients with pancreatic cancer. *Clin Gastroenterol Hepatol* [Internet] 20201105th ed. 20 (2): e196–227. Available from https://www.ncbi.nlm.nih.gov/pubmed/33161160.

Komuta, M., Govaere, O., Vandecaveye, V. et al. (2012). Histological diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes. *Hepatology* 55 (6): 1876–1888.

Koshiol, J., Gao, Y.T., Dean, M. et al. (2017 August). Association of Aflatoxin and Gallbladder cancer. *Gastroenterology* 153 (2): 488–494.e1.

Koshiol, J., Wozniak, A., Cook, P. et al. (2016 November). Salmonella enterica serovar Typhi and gallbladder cancer: a case-control study and meta-analysis. *Cancer Med* 5 (11): 3235–3310.

Kubo, S., Nagano, H., Tsujie, M. et al. (2022 August 19). Microsatellite instability in patients with hepato-biliary-pancreatic malignancies in clinical practice (KHBO 1903). *Int J Clin Oncol* 27 (8): 1340–1347.

Kubo, S., Takemura, S., Tanaka, S. et al. (2016). Screening and surveillance for occupational cholangiocarcinoma in workers exposed to organic solvents. *Surg Today* 46 (6): 705–712.

Kubo, S., Takemura, S., Tanaka, S. et al. (2018 March). Occupational cholangiocarcinoma caused by exposure to 1,2-dichloropropane and/or dichloromethane. *Ann Gastroenterol Surg* 2 (2): 99–105.

Kumagai, S., Kurumatani, N., Arimoto, A., and Ichihara, G. (2013 July). Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. *Occup Environ Med* 70 (7): 508–510.

Kusters, J.G., van Vliet, A.H.M., and Kuipers, E.J. (2006 July). Pathogenesis of Helicobacter pylori infection. *Clin Microbiol Rev* 19 (3): 449–490.

Labib, P.L., Goodchild, G., and Pereira, S.P. (2019 February). Molecular pathogenesis of cholangiocarcinoma. *BMC Cancer* 19 (1): 185.

Laird, B.J.A., Fallon, M., Hjermstad, M.J. et al. (2016 August 10). Quality of life in patients with advanced cancer: differential association with performance status and systemic inflammatory response. *Clin Oncol* 34 (23): 2769–2775.

Lang, S.A., Bednarsch, J., Joechle, K. et al. (2021 May 4). Prognostic biomarkers for cholangiocarcinoma (CCA): state of the art. *Expert Rev Gastroenterol Hepatol* 15 (5): 497–510.

Lapitz, A., Arbelaiz, A., O'Rourke, C.J. et al. (2020 March). Patients with cholangiocarcinoma present specific RNA profiles in serum and urine extracellular vesicles mirroring the tumor expression: novel liquid biopsy biomarkers for disease diagnosis. *Cells* 9 (3).

Lapitz, A., Arbelaiz, A., Olaizola, P. et al. (2018 October 12). Extracellular vesicles in hepatobiliary malignancies. *Front Immunol* 9: 2270.

Ledbetter, M.L.S. and Hotchkiss, R.D. (1975 August 20). Chromosomal Basis of the Merozygosity in a Partially Diploid Mutant of Pneumococcus. *Genetics* 80 (4): 667–678.

Leelawat, K., Narong, S., Wannaprasert, J., and Ratanashu-Ek, T. (2010). Prospective study of MMP7 serum levels in the diagnosis of cholangiocarcinoma. *World J Gastroenterol: WJG* 16 (37): 4697.

Levy, C., Lymp, J., Angulo, P. et al. (2005 September). The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. *Dig Dis Sci* 50 (9): 1734–1740.

Li, L., Masica, D., Ishida, M. et al. (2014 September). Human bile contains microRNA-laden extracellular vesicles that can be used for cholangiocarcinoma diagnosis. *Hepatology* 60 (3): 896–907.

Li, Y., Huang, Y., and Chen, J. (2019). Diagnostic value of serum biomarkers for intrahepatic cholangiocarcinoma. *J Coll Physicians Surg Pak* 29 (10): 962–966.

Liang, Z., Liu, X., Zhang, Q. et al. (2016 October 1). Diagnostic value of microRNAs as biomarkers for cholangiocarcinoma. *Dig. Liver Dis* 48 (10): 1227–1232.

Lin, H.Z., Zhang, T., Chen, M.Y., and Shen, J.L. (2021 February 22). Novel biomarkers for the diagnosis and prognosis of gallbladder cancer. *J Dig Dis* 22 (2): 62–71.

Liu, F., Wang, J., Ma, W. et al. (2019). Clinical value of preoperative CA19-9 levels in evaluating resectability of gallbladder carcinoma. *ANZ J Surg* 89 (3): E76–80.

Lodi, C., Szabo, E., Holczbauer, A. et al. (2006). Claudin-4 differentiates biliary tract cancers from hepatocellular carcinomas. *Modern Pathol* 19 (3): 460–469.

Loosen, S.H., Roderburg, C., Kauertz, K.L. et al. (2017 October). Elevated levels of circulating osteopontin are associated with a poor survival after resection of cholangiocarcinoma. *J Hepatol* 67 (4): 749–757.

Lowenfels, A.B. and Maisonneuve, P. (2006 April). Epidemiology and risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol* 20 (2): 197–209.

Lu, J., Li, B., Li, F. et al. (2019). Prognostic significance of mucinous component in hilar cholangiocarcinoma after curative-intent resection. *J Surg Oncol* 120 (8): 1341–1349.

Lu, M. and Zhan, X. (2018). The crucial role of multiomic approach in cancer research and clinically relevant outcomes. *EPMA J* 9 (1): 77–102.

Lugo, A., Peveri, G., Bosetti, C. et al. (2018). Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: a comprehensive review and meta-analysis. *Eur J Cancer* [Internet] 20181019th ed. 104: 117–126. Available from https://www.ncbi.nlm.nih.gov/pubmed/30347287.

Luo, G., Jin, K., Deng, S. et al. (2021 April). Roles of CA19-9 in pancreatic cancer: biomarker, predictor and promoter. *Biochim Biophys Acta - Rev Cancer* 1875 (2): 188409.

Macias, R.I.R., Banales, J.M., Sangro, B. et al. (2018 April). The search for novel diagnostic and prognostic biomarkers in cholangiocarcinoma. *Biochim Biophys Acta Mol Basis Dis* 1864 (4Pt B): 1468–1477.

Macias, R.I.R., Kornek, M., Rodrigues, P.M. et al. (2019 May 20). Diagnostic and prognostic biomarkers in cholangiocarcinoma. *Liver Int* 39 (S1): 108–122.

Mahdavifar, N., Mohammadian, M., and Salehiniya, H. (2018). Gallbladder cancer in the world: epidemiology, incidence, mortality and risk factors. *WCRJ* 1032113/wcrj_20189_1124 5 (3): e1124.

Maisonneuve, P. and Lowenfels, A.B. (2015 February 1). Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol* 44 (1): 186–198.

Maitra, A., Sharma, A., Brand, R.E. et al. (2018). A prospective study to establish a new-onset diabetes Cohort: from the consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer. *Pancreas* [Internet] 47 (10): 1244–1248. Available from https://www.ncbi.nlm.nih.gov/pubmed/30325864.

Makiuchi, T., Sobue, T., Kitamura, T. et al. (2019 May 5). Smoking, alcohol consumption, and risks for biliary tract cancer and intrahepatic bile duct cancer. *J Epidemiol* 29 (5): 180–186.

Makkar, R., Butt, J., Huang, W.Y. et al. (2020). Seropositivity for Helicobacter pylori and hepatobiliary cancers in the PLCO study. *Br J Cancer* 123 (6): 909–911.

Marcano-Bonilla, L., Mohamed, E.A., Mounajjed, T., and Roberts, L.R. (2016 October). Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. *Chin Clin Oncol* 5 (5): 61–61.

Marchegiani, G., Andrianello, S., Malleo, G. et al. (2017 July). Does size matter in pancreatic cancer? *Ann Surg* 266 (1): 142–148.

Masia, R. and Misdraji, J. (2018). Liver and bile duct infections. *Diagn Patho Infect Dis* 272–322.

Matsuda, Y. (2019). Age-related morphological changes in the pancreas and their association with pancreatic carcinogenesis. *Pathol Int* [Internet] 20190724th ed. 69 (8): 450–462. Available from https://www.ncbi.nlm.nih.gov/pubmed/31339204.

McFaul, C.D. (2006 February 1). Anticipation in familial pancreatic cancer. *Gut* 55 (2): 252–258.

McGee, E.E., Jackson, S.S., Petrick, J.L. et al. (2019 December 1). Smoking, alcohol, and biliary tract cancer risk: a pooling project of 26 prospective studies. *JNCI: J Natl Cancer Inst* 111 (12): 1263–1278.

Megibow, A.J., Baker, M.E., Morgan, D.E. et al. (2017 July). Management of incidental pancreatic cysts: a white paper of the ACR incidental findings committee. *J Am Coll Radiol* 14 (7): 911–923.

Merz, V., Zecchetto, C., Santoro, R. et al. (2020 September 1). Plasma IL8 is a biomarker for TAK1 activation and predicts resistance to nanoliposomal irinotecan in patients with gemcitabine-refractory pancreatic cancer. *Clinical Cancer Research* 26 (17): 4661–4669.

Midha, S., Chawla, S., and Garg, P.K. (2016 October). Modifiable and non-modifiable risk factors for pancreatic cancer: a review. *Cancer Lett* 381 (1): 269–277.

Moeini, A., Haber, P.K., and Sia, D. (2021 April). Cell of origin in biliary tract cancers and clinical implications. *JHEP Rep* 3 (2): 100226.

Molina-Montes, E., van Hoogstraten, L., Gomez-Rubio, P. et al. (2020). Pancreatic cancer risk in relation to lifetime smoking patterns, tobacco type, and dose-response relationships. *Cancer Epidemiol Biomarkers Prev* [Internet] 20200212th ed. 29 (5): 1009–1018. Available from https://www.ncbi.nlm.nih.gov/pubmed/32051190.

Morimoto, M., Matsuo, T., and Mori, N. (2021 June). Management of porcelain gallbladder, its risk factors, and complications: a review. *Diagnostics (Basel)* 11 (6).

Moss, E.L., Hollingworth, J., and Reynolds, T.M. (2005 March). The role of CA125 in clinical practice. *J Clin Pathol* 58 (3): 308–312.

Muñoz-Martínez, S., Rimola, J., Londoño, M.C. et al. (2022). Cholangiocarcinoma: early detection and screening in high-risk population. *Hepatoma Res* 8: 30.

Nagata, N., Nishijima, S., Kojima, Y. et al. (2022). Metagenomic identification of microbial signatures predicting pancreatic cancer from a multinational study. *Gastroenterology* [Internet] 20220408th ed. 163 (1): 222–238. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35398347.

Oldfield, L., Evans, A., Rao, R.G. et al. (2022). Blood levels of adiponectin and IL-1Ra distinguish type 3c from type 2 diabetes: implications for earlier pancreatic cancer detection in new-onset diabetes. *EBioMedicine* [Internet] 20220103rd ed. 75: 103802. Available from https://www.ncbi.nlm.nih.gov/pubmed/34990893.

Olthof, S.C., Othman, A., Clasen, S. et al. (2016 Dec). Imaging of Cholangiocarcinoma. *Visc Med* 32 (6): 402–410.

Ormanns, S., Haas, M., Baechmann, S. et al. (2016 December 1). Impact of SPARC expression on outcome in patients with advanced pancreatic cancer not receiving nab-paclitaxel: a pooled analysis from prospective clinical and translational trials. *Br J Cancer* 115 (12): 1520–1529.

Osataphan, S., Mahankasuwan, T., and Saengboonmee, C. (2021 December 17). Obesity and cholangiocarcinoma: a review of epidemiological and molecular associations. *J Hepatobiliary Pancreat Sci* 28 (12): 1047–1059.

Owens, D.K., Davidson, K.W., Krist, A.H. et al. (2019 August 6). Screening for pancreatic cancer. *JAMA* 322 (5): 438.

Pannala, R., Leirness, J.B., Bamlet, W.R. et al. (2008). Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus.

Gastroenterology [Internet] 20080118th ed. 134 (4): 981–987. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18395079.

Park, J.H., Han, K., Hong, J.Y. et al. (2022). Association between alcohol consumption and pancreatic cancer risk differs by glycaemic status: a nationwide cohort study. *Eur J Cancer* [Internet] 20220119th ed. 163: 119–127. Available from https://www.ncbi.nlm.nih.gov/pubmed/35065369.

Patel, A.H., Harnois, D.M., Klee, G.G. et al. (2000). The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. *Am J Gastroenterol* 95 (1): 204–207.

Patel, T. (2011 April). Cholangiocarcinoma–controversies and challenges. *Nat Rev Gastroenterol Hepatol* 8 (4): 189–200.

Pereira, S.P., Oldfield, L., Ney, A. et al. (2020 July). Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol* 5 (7): 698–710. Available from https://www.ncbi.nlm.nih.gov/pubmed/32135127.

Perkhofer, L., Gout, J., Roger, E. et al. (2021 March). DNA damage repair as a target in pancreatic cancer: state-of-the-art and future perspectives. *Gut* 70 (3): 606–617.

Permert, J., Ihse, I., Jorfeldt, L. et al. (1993). Pancreatic cancer is associated with impaired glucose metabolism. *Eur J Surg* [Internet] 159 (2): 101–107. Available from https://www.ncbi.nlm.nih.gov/pubmed/8098623.

Phyo Myint, E.E., Sereemaspun, A., Rocklöv, J., and Nithikathkul, C. (2020 June). Discovery of carcinogenic liver fluke metacercariae in second intermediate hosts and surveillance on fish-borne trematode metacercariae infections in Mekong region of Myanmar. *Int J Environ Res Public Health* 17 (11).

Pinter, M., Trauner, M., Peck-Radosavljevic, M., and Sieghart, W. (2016). Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open* 1 (2): 1–16.

Porta, M., Gasull, M., Pumarega, J. et al. (2022). Plasma concentrations of persistent organic pollutants and pancreatic cancer risk. *Int J Epidemiol* [Internet] 51 (2): 479–490. Available from https://www.ncbi.nlm.nih.gov/pubmed/34259837.

Portincasa, P., van Erpecum, K.J., Di Ciaula, A., and Wang, D.Q.H. (2019 February 1). The physical presence of gallstone modulates ex vivo cholesterol crystallization pathways of human bile. *Gastroenterol Rep (Oxf)* 7 (1): 32–41.

Postlewait, L.M., Ethun, C.G., McInnis, M.R. et al. (2017 January 1). Association of preoperative risk factors with malignancy in pancreatic mucinous cystic neoplasms. *JAMA Surg* 152 (1): 19.

Proca, D.M., Niemann, T.H., Porcell, A.I., and DeYoung, B.R. (2000). MOC31 immunoreactivity in primary and metastatic carcinoma of the liver: report of findings and review of other utilized markers. *Appl Immunohistochem Mol Morphol* 8 (2): 120–125.

Prueksapanich, P., Piyachaturawat, P., Aumpansub, P. et al. (2018 May). Liver fluke-associated biliary tract cancer. *Gut Liver* 12 (3): 236–245.

Puleo, F., Nicolle, R., Blum, Y. et al. (2018 December). Stratification of pancreatic ductal adenocarcinomas based on tumor and microenvironment features. *Gastroenterology* 155 (6): 1999–2013.e3.

Qin, D. (2019 February). Next-generation sequencing and its clinical application. *Cancer Biol Med* 16 (1): 4–10.

Qureshi, T.A., Gaddam, S., Wachsman, A.M. et al. (2022). Predicting pancreatic ductal adenocarcinoma using artificial intelligence analysis of pre-diagnostic computed tomography images. *Cancer Biomark* 33(2): 211–217. doi: 10.3233/CBM-210273.

Rabiee, A. and Silveira, M.G. (2021). Primary sclerosing cholangitis. *Transl Gastroenterol Hepatol* 6: 29.

Rahnemai-Azar, A.A., Weisbrod, A., Dillhoff, M. et al. (2017 June). Intrahepatic cholangiocarcinoma: molecular markers for diagnosis and prognosis. *Surg Oncol* 26 (2): 125–137.

Rajasegaran, Y., Azlan, A., Rosli, A.A. et al. (2021 October). Footprints of microRNAs in cancer biology. *Biomedicines* 9 (10).

Rana, S., Dutta, U., Kochhar, R. et al. (2012). Evaluation of CA 242 as a tumor marker in gallbladder cancer. *J Gastrointest Cancer* 43 (2): 267–271.

Rawla, P., Sunkara, T., and Gaduputi, V. (2019). Epidemiology of pancreatic cancer: global trends, etiology and risk factors. *World J Oncol* 10 (1): 10–27.

Rawla, P., Sunkara, T., Thandra, K.C., and Barsouk, A. (2019 May). Epidemiology of gallbladder cancer. *Clin Exp Hepatol* 5 (2): 93–102.

Rizvi, S., Eaton, J., Yang, J.D. et al. (2018 May). Emerging technologies for the diagnosis of Perihilar Cholangiocarcinoma. *Semin Liver Dis* 38 (2): 160–169.

Rodrigues, P.M., Perugorria, M.J., Santos-Laso, A. et al. (2018). Primary biliary cholangitis: a tale of epigenetically-induced secretory failure? *J Hepatol* 69 (6): 1371–1383.

Rule, A.H., Goleski-Reilly, C., Sachar, D.B. et al. (1973 November). Circulating carcinoembryonic antigen (CEA): relationship to clinical status of patients with inflammatory bowel disease. *Gut* 14 (11): 880–884.

Saffioti, F. and Mavroeidis, V.K. (2021 October). Review of incidence and outcomes of treatment of cholangiocarcinoma in patients with primary sclerosing cholangitis. *World J Gastrointest Oncol* 13 (10): 1336–1366.

Sala, M., Ros, M., and Saltel, F. (2020). A complex and evolutive character: two face aspects of ECM in tumor progression. *Front Oncol* 10: 1620.

Satiya, J., Mousa, O.Y., Gupta, K. et al. (2020 February). Diagnostic yield of magnetic resonance imaging for cholangiocarcinoma in primary sclerosing cholangitis: a meta-analysis. *Clin Exp Hepatol* 6 (1): 35–41.

Schauer, D.P., Feigelson, H.S., Koebnick, C. et al. (2019). Bariatric surgery and the risk of cancer in a large multisite Cohort. *Ann Surg* [Internet] 269 (1): 95–101. Available from https://www.ncbi.nlm.nih.gov/pubmed/28938270.

Schmidt-Hansen, M., Berendse, S., and Hamilton, W. (2016 July). Symptoms of pancreatic cancer in primary care. *Pancreas* 45 (6): 814–818.

Segura-López, F.K., Güitrón-Cantú, A., and Torres, J. (2015 February). Association between Helicobacter spp. infections and hepatobiliary malignancies: a review. *World J Gastroenterol* 21 (5): 1414–1423.

Sharma, A., Kandlakunta, H., Nagpal, S.J.S. et al. (2018). Model to determine risk of pancreatic cancer in patients with new-onset diabetes. *Gastroenterology* [Internet] 20180611th ed. 155 (3): 730–739.e3. Available from https://www.ncbi.nlm.nih.gov/pubmed/29775599.

Sharma, A., Smyrk, T.C., Levy, M.J. et al. (2018). Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. *Gastroenterology* [Internet] 20180430th ed. 155 (2): 490–500.e2. Available from https://www.ncbi.nlm.nih.gov/pubmed/29723506.

Sharma, J., Huda, F., Naithani, M. et al. (2022). Role of Gut Microbiome and Enteric Bacteria in Gallbladder Cancer. *Immunology of the GI Tract - Recent Advances*. IntechOpen. doi: 10.5772/intechopen.104404.

Shen, N., Zhang, D., Yin, L. et al. (2019). Bile cell-free DNA as a novel and powerful liquid biopsy for detecting somatic variants in biliary tract cancer. *Oncol Rep* 42 (2): 549–560.

Sheth, S.G., Conwell, D.L., Whitcomb, D.C. et al. (2017 May). Academic pancreas centers of excellence: guidance from a multidisciplinary chronic pancreatitis working group at PancreasFest. *Pancreatology* 17 (3): 419–430.

Shieh, Y., Eklund, M., Sawaya, G.F. et al. (2016 September 13). Population-based screening for cancer: hope and hype. *Nat Rev Clin Oncol* 13 (9): 550–565.

Signoretti, M., Bruno, M.J., Zerboni, G. et al. (2018 May). Results of surveillance in individuals at high-risk of pancreatic cancer: a systematic review and meta-analysis. *United Eur Gastroenterol J* 6 (4): 489–499.

Silakit, R., Loilome, W., Yongvanit, P. et al. (2017). Urinary microRNA-192 and microRNA-21 as potential indicators for liver fluke-associated cholangiocarcinoma risk group. *Parasitol Int* 66 (4): 479–485.

Singhi, A.D., Koay, E.J., Chari, S.T., and Maitra, A. (2019). Early detection of pancreatic cancer: opportunities and Challenges. *Gastroenterology* 156 (7): 2024–2040.

Siripongsakun, S., Vidhyarkorn, S., Charuswattanakul, S. et al. (2018 July). Ultrasound surveillance for cholangiocarcinoma in an endemic area: a prove of survival benefits. *J Gastroenterol Hepatol* 33 (7): 1383–1388.

Sithithaworn, P., Andrews, R.H., Nguyen, V.D. et al. (2012 March). The current status of opisthorchiasis and clonorchiasis in the Mekong Basin. *Parasitol Int* 61 (1): 10–16.

Sombattheera, S., Proungvitaya, T., Limpaiboon, T. et al. (2015). Total serum bile acid as a potential marker for the diagnosis of cholangiocarcinoma without jaundice. *Asian Pac J Cancer Prev* 16 (4): 1367–1370.

Song, J., Li, Y., Bowlus, C.L. et al. (2020 February 28). Cholangiocarcinoma in patients with Primary Sclerosing Cholangitis (PSC): a comprehensive review. *Clin Rev Allergy Immunol* 58 (1): 134–149.

Srivastava, A. and Creek, D.J. (2019 May). Discovery and validation of clinical biomarkers of cancer: a review combining metabolomics and proteomics. *Proteomics* 19 (10, SI).

Stapley, S., Peters, T.J., Neal, R.D. et al. (2012 June 22). The risk of pancreatic cancer in symptomatic patients in primary care: a large case–control study using electronic records. *Br J Cancer* 106 (12): 1940–1944.

Stein, M., Ruggiero, P., Rappuoli, R., and Bagnoli, F. (2013 October). Helicobacter pylori CagA: from pathogenic mechanisms to its use as an anti-cancer vaccine. *Front Immunol* 4: 328.

Stinton, L.M. and Shaffer, E.A. (2012 April). Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver* 6 (2): 172–187.

Subrungruanga, I., Thawornkunob, C., Chawalitchewinkoon-Petmitrc, P. et al. (2013). Gene expression profiling of intrahepatic cholangiocarcinoma. *Asian Pac J Cancer Prev* 14 (1): 557–563.

Sun, C., Zhu, J., Wu, B. et al. (2018). Diagnostic and prognostic value of microRNAs in cholangiocarcinoma: a systematic review and meta-analysis. *Cancer Manag Res* 10: 2125–2139.

Sung, H., Ferlay, J., Siegel, R.L. et al. (2021 May 4). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin* 71 (3): 209–249.

Sung, J.J., Ho, J.M., Lam, A.S. et al. (2020). Use of metformin and aspirin is associated with delayed cancer incidence. *Cancer Epidemiol* [Internet] 20200909th ed. 69: 101808. Available from https://www.ncbi.nlm.nih.gov/pubmed/32919225.

Sungkasubun, P., Siripongsakun, S., Akkarachinorate, K. et al. (2016 June). Ultrasound screening for cholangiocarcinoma could detect premalignant lesions and early-stage diseases with survival benefits: a population-based prospective study of 4,225 subjects in an endemic area. *BMC Cancer* 16: 346.

Takahashi, Y., Dungubat, E., Kusano, H. et al. (2021). Application of immunohistochemistry in the pathological diagnosis of liver tumors. *Int J Mol Sci* 22 (11): 5780.

Tan, N., Ngu, N., Worland, T. et al. (2022 June 3). Epidemiology and outcomes of primary sclerosing cholangitis: an Australian multicentre retrospective cohort study. *Hepatol Int* 16: 1094–1104. doi: 10.1007/s12072-022-10356-1.

Tanaka, M., Fernández-del Castillo, C., Kamisawa, T. et al. (2017 September). Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology* 17 (5): 738–753.

Tariq, N.U.A., McNamara, M.G., and Valle, J.W. (2019). Biliary tract cancers: current knowledge, clinical candidates and future challenges. *Cancer Manag Res* 11: 2623–2642.

Tezuka, S., Ueno, M., Kobayashi, S. et al. (2018). Predictive value of ERCC1, ERCC2, ERCC4, and glutathione S-Transferase Pi expression for the efficacy and safety of FOLFIRINOX in patients with unresectable pancreatic cancer. *Am J Cancer Res* 8 (10): 2096–2105.

Thompson, D., Duedal, S., Kirner, J. et al. (2005 June 1). Cancer risks and mortality in heterozygous ATM mutation carriers. *JNCI: J Natl Cancer Inst* 97 (11): 813–822.

Truty, M.J., Kendrick, M.L., Nagorney, D.M. et al. (2021 February). Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg* 273 (2): 341–349.

Tsoi, K.K.F., Ho, J.M.W., Chan, F.C.H., and Sung, J.J.Y. (2019). Long-term use of low-dose aspirin for cancer prevention: a 10-year population cohort study in Hong Kong. *Int J Cancer* [Internet] 20190107th ed. 145 (1): 267–273. Available from https://www.ncbi.nlm.nih.gov/pubmed/30575949.

Turati, F., Edefonti, V., Bosetti, C. et al. (2013 October). Family history of cancer and the risk of cancer: a network of case–control studies. *Ann Oncol* 24 (10): 2651–2656.

Turati, F., Rossi, M., Mattioli, V. et al. (2022). Diabetes risk reduction diet and the risk of pancreatic cancer. *Eur J Nutr* [Internet] 20210802nd ed. 61 (1): 309–316. Available from https://www.ncbi.nlm.nih.gov/pubmed/34338866.

Valle, J.W., Kelley, R.K., Nervi, B. et al. (2021 January). Biliary tract cancer. *Lancet* 397 (10272): 428–444.

Valle, J.W., Lamarca, A., Goyal, L. et al. (2017 September). New horizons for precision medicine in biliary tract cancers. *Cancer Discov* 7 (9): 943–962.

van Dongen, J.C., van der Geest, L.G.M., de Meijer, V.E. et al. (2022 March 4). Age and prognosis in patients with pancreatic cancer: a population-based study. *Acta Oncol (Madr)* 61 (3): 286–293.

van Huijgevoort, N.C.M., Del Chiaro, M., Wolfgang, C.L. et al. (2019 November 16). Diagnosis and management of pancreatic cystic neoplasms: current evidence and guidelines. *Nat Rev Gastroenterol Hepatol* 16 (11): 676–689.

Vege, S.S., Ziring, B., Jain, R. et al. (2015 April). American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 148 (4): 819–822.

Vincent, A., Herman, J., Schulick, R. et al. (2011 August). Pancreatic cancer. *Lancet* 378 (9791): 607–620.

Vithayathil, M. and Khan, S.A. (2022). Current epidemiology of cholangiocarcinoma in Western countries. *J hepatol* 77 (6): 1690–1698. doi: 10.1016/j.jhep.2022.07.022.

Voigtländer, T., Gupta, S.K., Thum, S. et al. (2015 April 1). MicroRNAs in serum and bile of patients with primary sclerosing cholangitis and/or cholangiocarcinoma. *J Hepatol* 62: S795–6.

Vujasinovic, M., Zaletel, J., Tepes, B. et al. (2013). Low prevalence of exocrine pancreatic insufficiency in patients with diabetes mellitus. *Pancreatology* [Internet] 20130614th ed. 13 (4): 343–346. Available from https://www.ncbi.nlm.nih.gov/pubmed/23890131.

Waddell, N., Pajic, M., Patch, A.M. et al. (2015 February 26). Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 518 (7540): 495–501.

Wang, L.J., He, C.C., Sui, X. et al. (2015 March). MiR-21 promotes intrahepatic cholangiocarcinoma proliferation and growth in vitro and in vivo by targeting PTPN14 and PTEN. *Oncotarget* 6 (8): 5932–5946.

Wang, M., Wang, Y., Feng, X. et al. (2017). Contribution of hepatitis B virus and hepatitis C virus to liver cancer in China north areas: experience of the Chinese national cancer center. *Int J Infect Dis* 65: 15–21.

Wang, S., Chen, Y., Xu, X. et al. (2017 November). Prevalence of hepatitis B virus and hepatitis C virus infection in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Oncotarget* 8 (60): 102437–102445.

Wang, Y., Lu, J., Wen, N. et al. (2022 December 30). The role of diet and nutrition related indicators in biliary diseases: an umbrella review of systematic review and meta-analysis. *Nutr Metab (Lond)* 19 (1): 51.

Wang, Y.F., Feng, F.L., Zhao, X.H. et al. (2014). Combined detection tumor markers for diagnosis and prognosis of gallbladder cancer. *World J Gastroenterol: WJG* 20 (14): 4085.

Wang, Y.T., Gou, Y.W., Jin, W.W. et al. (2016). Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies. *BMC Cancer* [Internet] 20160312th ed. 16: 212. Available from https://www.ncbi.nlm.nih.gov/pubmed/26968702.

Wardell, C.P., Fujita, M., Yamada, T. et al. (2018). Genomic characterization of biliary tract cancers identifies driver genes and predisposing mutations. *J Hepatol* 68 (5): 959–969.

Woodmansey, C., McGovern, A.P., McCullough, K.A. et al. (2017). Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (Type 3c): a retrospective cohort study. *Diabetes Care* [Internet] 20170831st ed. 40 (11): 1486–1493. Available from https://www.ncbi.nlm.nih.gov/pubmed/28860126.

Wörmann, B., Bokemeyer, C., Burmeister, T. et al. (2020). Dihydropyrimidine dehydrogenase testing prior to treatment with 5-Fluorouracil, Capecitabine, and Tegafur: a consensus paper. *Oncol Res Treat* 43 (11): 628–636.

Yang, F., Wan, Y., Xu, L. et al. (2021). MRI-Radiomics prediction for cytokeratin 19-Positive hepatocellular carcinoma: a multicenter study. *Front Oncol* 3081.

Yang, J.D., Campion, M.B., Liu, M.C. et al. (2016). Circulating tumor cells are associated with poor overall survival in patients with cholangiocarcinoma. *Hepatology* 63 (1): 148–158.

Ye, Y., Lui, V.C.H., and Tam, P.K.H. (2022). Pathogenesis of choledochal cyst: insights from genomics and transcriptomics. *Genes (Basel)* 13 (6): 1030.

Yuan, C., Kim, J., Wang, Q.L. et al. (2022). The age-dependent association of risk factors with pancreatic cancer. *Ann Oncol* [Internet] 20220406th ed. 33 (7): 693–701. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35398288.

Zerboni, G., Signoretti, M., Crippa, S. et al. (2019 January). Systematic review and meta-analysis: prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals. *Pancreatology* 19 (1): 2–9.

Zhao, H., Wu, L., Yan, G. et al. (2021). Inflammation and tumor progression: signaling pathways and targeted intervention. *Signal Transduct Target Ther* 6 (1).

Zhou, J., Liu, Z., Yang, S., and Li, X. (2017 March). Identification of microRNAs as biomarkers for cholangiocarcinoma detection: a diagnostic meta-analysis. *Clin Res Hepatol Gastroenterol* 41 (2): 156–162.

18 The Multidisciplinary Management of Primary Hepatocellular Carcinoma

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Introduction

Hepatocellular cancer (HCC) remains one of the fastest growing causes of cancer-related deaths in the United States and is the leading cause of deaths overall in patients with cirrhosis (Ioannou et al. 2007). In 2020, HCC was the sixth commonest cancer diagnosis worldwide, with approximately 906,000 new cases (Sung et al. 2021). In men, liver cancer was the second most frequently occurring cancer death (Sung et al. 2021).

Who Is at Risk of Developing Hepatocellular Carcinoma?

The vast majority of HCC arises in those with underlying chronic liver disease, including cirrhosis of any cause, chronic viral hepatitis B, and advanced non-alcoholic fatty liver disease with advanced fibrosis (Table 1) (Liu et al. 2019). This allows clear identification of the at-risk population in whom screening for HCC should be implemented.

How Do We Stage Hepatocellular Carcinoma?

The most well-recognized staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging classification (Table 2) (Llovet et al. 1999a). The BCLC staging is preferred over the TNM staging system as it encompasses the severity of the underlying liver disease which strongly affects prognosis, defined using the Child-Pugh classification system (Table 3). Factors which affect prognosis include bilirubin level, presence of portal hypertension, presence of portal vein thrombus, presence of extrahepatic spread, presence of constitutional symptoms, and patient's performance status (Llovet et al. 1999b). Most of these factors are accounted for in the BCLC staging system except performance status. The stage of HCC and patient's functional status (Table 4) dictate the intent and type of treatment that should be offered.

Locoregional Therapy

Case: A 75-year-old male has a history of alcoholic and NASH Child-Pugh A cirrhosis. He is independent with his mobility and activities of daily living. His HCC surveillance prompted a multiphase CT that revealed a solitary enhancing 56 mm nodule in Segment IV (Figure 1). However, he was found to have features of severe portal hypertension on imaging (Figure 2). His case was discussed at an MDT meeting and it was deemed his portal hypertension precluded surgical resection. Instead, he proceeded to TACE of which he had two sessions, with imaging confirming a favorable response. After re-discussion at the MDT meeting, the interventional radiologist had concerns of a possible cystic artery supply to the lesion, so it was decided that the patient would benefit further from MWA to ensure treatment completion.

What Is Transarterial Embolization?

Transarterial Embolization (TAE) or Transarterial Chemoembolization (TACE) is a widely utilized therapy for the

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treatment of intermediate stage HCC who have well-preserved liver function and a large or multinodular HCC without portal vein tumor thrombosis or extrahepatic metastasis, as outlined in the patient case seen earlier. A survival advantage compared to best supportive care has been clearly demonstrated across a number of studies for patients receiving TACE in this cohort (Lencioni et al. 2016; Llovet et al. 2002; Llovet and Bruix 2003). Nearly half of all HCC patients worldwide receive TACE at some point in the course of their disease (Lencioni et al. 2014).

Table 1 Causes of liver cirrhosis.

Causes of liver cirrhosis
Non-alcoholic fatty liver disease
Alcohol related liver disease
Viral
Hepatitis B
Hepatitis C
Autoimmune
Primary biliary cholangitis
Primary sclerosing cholangitis
Autoimmune hepatitis
Infiltrative/metabolic
Haemochromatosis
Wilson’s disease
Alpha-1-antitrypsin deficiency
Granulomatous liver disease
Polycystic liver disease
Other
Medications
Hereditary hemorrhagic telangiectasia

There is wide heterogeneity in technique with variations which include Conventional Transarterial Chemoembolization (cTACE), Bland Embolization and Drug Eluting Beads TACE (DEB-TACE).

cTACE is the most commonly performed variation. The rationale of cTACE is to occlude the blood supply to the hypervascular HCC with an emulsion of lipidol and a chemotherapeutic agent, most commonly doxorubicin or cisplatin. As HCC derives its vascular supply from the hepatic artery, as opposed to the non-tumor liver parenchyma, occlusion results in necrosis and slows tumor progression (Au and Frenette 2015; Piscaglia and Ogasawara 2018). The treatment can be performed with a lobar, segmental, or super selective approach. Common adverse effects include post embolization syndrome, liver enzyme abnormalities (18.1%), fever (17.2%), abdominal pain (11.0%), vomiting (6.0%), and nausea (1.7%) (Piscaglia and Ogasawara 2018).

Bland embolization is performed in a small number of highly experienced centers. Bland embolization is performed with particles to cause ischemia by cutting off the blood supply without a chemotherapeutic agent. Studies have indicated that there is no survival benefit of cTACE compared to bland embo-

Table 2 Barcelona Clinic Liver Cancer (BCLC) staging system.

BCLC stage	Description	Child-Pugh Class	Treatment
A (early stage)			
A1	Single tumor with normal bilirubin	A	Curative resection, percutaneous treatment, or liver transplantation
A2	Single tumor with normal bilirubin but portal hypertension present	A–B	
A3	Single tumor with raised bilirubin and portal hypertension	A–B	
A4	Three tumors less than 3 cm in size	A–B	
B (intermediate stage)	Asymptomatic multinodular HCC	A–B	Palliative treatment
C (advanced stage)	Advanced symptomatic HCC with high risk features (vascular invasion, extrahepatic spread)	A–B	Systemic palliative treatment
D (end-stage)	End-stage widespread HCC	C	Best supportive care

Table 3 Child-Pugh classification system.

Clinical and lab criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate	Severe
Bilirubin (umol/L)	< 34	34–50	> 50
Albumin (g/L)	> 35	28–35	< 28
INR	< 1.7	1.7–2.3	> 2.3

Table 4 European Cooperative Oncology Group (ECOG) performance status classification system.

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair.

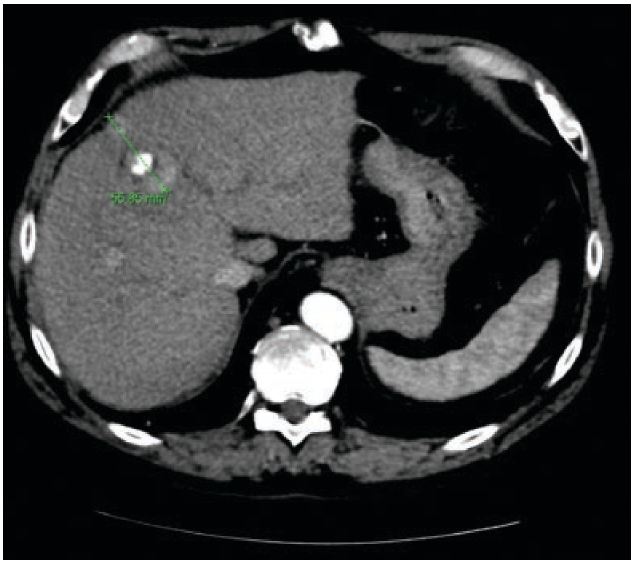

Figure 1 Arterially enhancing 56 mm nodule in segment 4 in a cirrhotic liver.

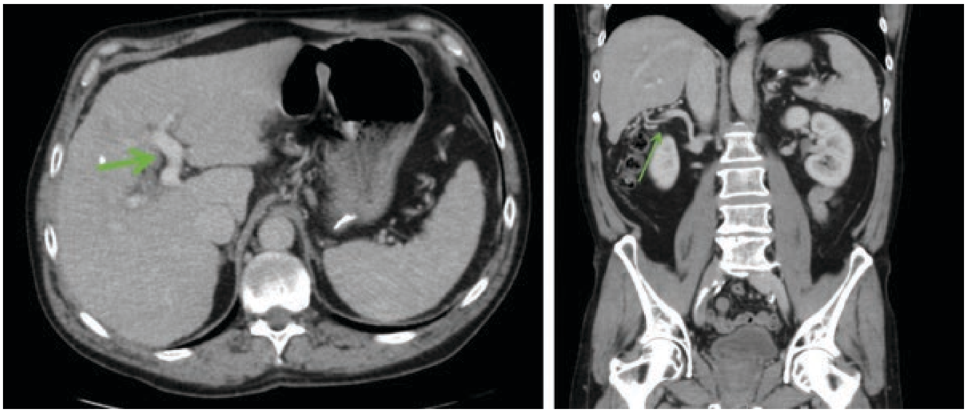

Figure 2 Dilation of portal vein with resultant varices in right upper quadrant, seen in portal venous phase.

lization and this remains an area of ongoing research (Brown et al. 2016; Maluccio et al. 2008).

Drug eluting beads (DEB) were developed to enhance the delivery of the chemotherapeutic agent. DEBs are microspheres which are loaded with a standardized dose of chemotherapeutic agent (most commonly doxorubicin) that allows for a slow release of the drug. The aim of this mechanism is to ensure high local and low systemic drug concentrations (Sieghart et al. 2015). In a subgroup analysis of patients with more advanced disease such as Child-Pugh B, ECOG 1, bilobar or recurrent disease DEB-TACE appears to outperform cTACE (Lammer et al. 2010).

What Is Transarterial Radioembolization?

Transarterial radioembolization (TARE) is a well-established locoregional therapy which has an expanding role in the treatment of HCC. It is a transarterial therapy which involves radioisotope-loaded particle embolization into the liver. The embolic particle does not occlude or alter the microvasculature of the hepatic artery due to its small size and thus is considered safe in portal vein thrombosis, unlike TACE. Its method of action is via local radiotherapy with increased significance given to its immunological effects (Chew et al. 2019). It is commonly infused via the hepatic artery into either a lobar or more recently, in a segmental distribution.

TARE requires a comprehensive preprocedural workup which includes assessment of the vascular anatomy and the hepato-pulmonary shunt. The workup involves a diagnostic angiogram to evaluate the vascular anatomy and embolize any extrahepatic branches which could lead to microsphere dispersion to non-target organs. In addition, the hepato-pulmonary shunt is determined at this diagnostic angiogram through the injection of macro aggregates of albumin (MAA) labeled with

Tc99. MAA-Tc99 behaves similarly to the radio-embolization microspheres and thus are used as a proxy to assess distribution to the lungs. A large shunt can lead to rare complications such as non-target pulmonary irradiation and radiation pneumonitis. A SPECT/CT is performed within an hour from the injection to assess the hepato-pulmonary shunt (Ilhan et al. 2015). Contra-indications include a hepato-pulmonary shunt >20% of the injected dose or vascular abnormalities not correctable by embolization.

In addition, radiation lobectomy can be considered for increasing the future liver remnant with similar volumetric improvements to portal vein embolization with the added benefit of local tumor control (Vouche et al. 2013). Rather than the conventional strategy of lobar Y90 infusion, selective radio embolization of the tumor-bearing hepatic segment has been recently employed, termed “radiation segmentectomy.” This method allows significantly higher radiation doses to be safely delivered to individual segments without compromising the non-tumor bearing liver parenchyma. Exceeding this new threshold dose (>400 mGy) for an ablative effect results in complete pathological necrosis of the tumor with survival outcomes similar to curative approaches such as resection and radiofrequency ablation (Salem et al. 2021).

When Do We Use TARE Over TACE?

Compared to TACE, TARE does not demonstrate a clear survival benefit for BCLC A/B patients; however there is improved time to progression and reduced toxicity (Salem et al. 2016). TARE is an effective bridging therapy to liver transplantation with evidence suggesting it is more effective than TACE (Ettorre et al. 2017; Lewandowski et al. 2009). In the newest guidelines, TARE should now be considered for single lesions ≤8 cm in BCLC 0/A patients if surgical resection and ablation is not technically feasible (Salem et al. 2021; Reig et al. 2022).

What Is Tumor Ablation?

Tumor ablation is a minimally invasive treatment that is commonly performed for the treatment of HCC; the primary endpoint is to obtain complete necrosis of tumors. Ablation is a keystone in the management of HCC with proven efficacy, especially for lesions <3 cm. It can be employed as a first line therapy, an alternative for surgery or in association with resection in patients with a poor functional liver reserve (FLR) (Benson et al. 2021; Izzo et al. 2019).

Most commonly thermal and chemical ablation are used for HCC. Thermal ablation techniques include microwave ablation (MWA) and radiofrequency ablation. Thermal ablation induces cell death by delivering a destructive local temperature change to the tumor to induce coagulative necrosis (Young and Golzarian 2020). RFA employs thermo coagulation necrosis whereas MWA utilizes dielectric heating. Thermal ablation is often performed percutaneously under image guidance by inserting a probe into the tumor. Ablation may also be performed laparoscopically or via open surgery. Chemical ablation involves injecting ethanol into a tumor to cause cell death.

MWA and RFA are the most commonly performed and clinically verified ablation techniques with well demonstrated efficacy and a safety profile (Alonzo et al. 2015; Reig et al. 2022). Ethanol ablation should be considered where these are not feasible or safe (Reig et al. 2022). MWA is a newer modality with advantages over RFA including a larger zone of active heating and a more uniform necrosis within the tumor compared to RFA (Izzo et al. 2019). Additionally as MWA is not limited by tissue conductance, it is less susceptible to the “heat sink effect” compared to RFA (Izzo et al. 2019). The heat sink effect is a phenomenon where the effectiveness of hyperthermic tumor ablation is impaired when flowing blood in a large adjacent vessel causes a cooling effect (Goldberg et al. 1998). Whilst there is a trend to suggest MWA may be more efficacious, studies to date have not demonstrated a statistically significant difference in overall survival between the two modalities (Vietti Violi et al. 2018; Yu et al. 2017). MWA does however lead to decreased procedure times and better tumor inactivation for tumors 3–5 cm, adjacent to vessels and the gallbladder (Facciorusso et al. 2016; Vietti Violi et al. 2018; Yu et al. 2017).

What about Combination Therapy of TACE-ablation?

As shown in our patient case, the combination of TACE-Ablation is an effective tool for 3–5 cm HCC with proven superiority over monotherapy and for patients bridging to transplant. There is emerging evidence that for 3–5 cm HCC, it has comparable outcomes to surgery. TACE decreases the vascularity of the treated area and allows for a larger, more efficacious, ablation zone to be created with high rates of histopathological necrosis (Vasnani et al. 2016; Young and Golzarian 2020). The TACE-Ablation combination has proven superiority compared to TACE or ablation alone in terms of overall survival and oncological outcomes (Ni et al. 2013; Peng et al. 2018). Additional benefits include that TACE prior to ablation will clearly delineate the tumor margins and reveal satellite lesions that may have been occult on preoperative imaging (Peng et al. 2018). There is emerging data suggesting it is comparable to surgery for overall survival and oncological outcomes (Kim et al. 2013; Lee et al. 2019; Peng et al. 2018). TACE-ablation is also an effective tool for bridging therapy to transplant (Vasnani et al. 2016).

For optimal oncological outcomes, a 1 cm margin is the standard of care. Thus the TACE-ablation combination however is dependent on a favorably located lesion due to the large ablation zone. TARE is often employed in this patient population however there is limited comparative data though TACE-ablation has been more extensively studied (Young et al. 2020).

Surgery

Case: A 56-year-old man of East Asian background is diagnosed with chronic hepatitis B after a full liver screen completed for deranged liver function tests. He is referred to a hepatologist who commences him on an antiviral agent and enrolls him to a HCC screen with six-monthly liver ultrasound and serum alpha-fetoprotein (AFP) levels. He is found to have a raised AFP level and a solitary 2-centimeter solid liver lesion in segment VIII, which is then confirmed to be HCC on a multiphase CT abdomen with characteristic arterial enhancement and venous washout (Figure 3). He is evaluated in a multidisciplinary meeting and undergoes curative liver resection. He continues to follow up in the liver clinic with ongoing antiviral therapy, monitoring of liver function tests and six-monthly HCC screen.

How Do We Decide Who Is Eligible for Surgery?

Many patients with HCC have underlying liver dysfunction which makes the surgical management so challenging. The chance of curative resection must be cautiously balanced with the risk of precipitating hepatic failure. In early-stage disease meeting evidence-based criteria, liver transplantation offers the ability to not only gain local control but also treat the underlying liver disease. However, the hindrance of graft shortages means that surgical resection remains the first-line treatment for early-stage disease in appropriate candidates and is safe and effective. Modern surgical approaches have achieved mortality rates of <3% with overall morbidity rates of <30% (Witowski et al. 2019). Most deaths are due to post-operative liver failure. To avoid this, patient selection is paramount and should be done using a multidisciplinary approach. Selection involves exploring the patient, tumor and surgical factors that may impact on peri- and post-operative outcomes. In the following section, we will explore these in turn.

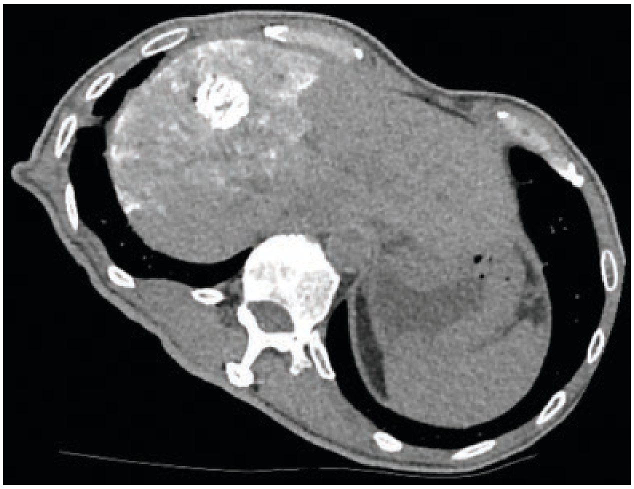

Figure 3 Arterially enhancing 2 cm nodule in segment 8 in a non-cirrhotic liver.

The following parameters need to be taken into account in the pre-operative assessment.

Patient Factors

General Health

Comorbid illnesses increase the risk of post-operative morbidity and mortality in patients undergoing liver surgery for HCC (Wei et al. 2003). Therefore, thorough pre-operative evaluation of the general health of patients is a crucial aspect of assessing their candidacy for liver resection, particularly in the context of cirrhosis. This evaluation must incorporate assessments of all major organs, particularly cardiac, respiratory, and renal functions. Thus, pre-operative assessment and optimization of pre-existing comorbidities and risk factors are important to minimize complications and help select patients appropriately for surgery.

Malnutrition and Sarcopenia

Malnutrition and sarcopenia are common in patients with cirrhosis as a result of protein catabolism (Perisetti et al. 2022). This can be compounded in patients with HCC. Patients with malnutrition and sarcopenia undergoing liver surgery for HCC are at a higher risk of post-operative complications, liver failure, and longer length of stay (Huang et al. 2019; Otsuji et al. 2015). Sarcopenia has also been associated with reduced total functional liver volume, as well as reduced five-year overall and recurrence-free survival (Dello et al. 2013). Nutritional therapy given prior to liver resection has been shown to reduce sepsis, need for treatment of ascites and overall post-operative morbidity and mortality rates (Fan et al. 1994). Identifying and quantifying malnutrition and sarcopenia in patients being considered for liver resection is important to allow adequate pre-operative nutritional optimization, aided by specialist dietetic advice.

Age

There is a significant age-specific increase in the development of HCC in those aged over 75 (El-Serag and Rudolph 2007). Liver resection in this cohort has historically been less favorable than locoregional therapies due to the perceived frailty that accompanies advanced age, as well as the increased number of comorbidities and likelihood of less physiological reserve to cope with complications (Cho et al. 2019). However, a number of retrospective studies have demonstrated similar three- or five-year overall and disease-free survival rates between elderly and younger patients undergoing liver resection for HCC

(Kishida et al. 2015; Nishikawa et al. 2013; Okamura et al. 2018; Santambrogio et al. 2017; Yamada et al. 2012; Wu et al. 2019). Therefore, older age should not be an absolute contraindication for surgery by itself and in highly selected elderly patients' hepatic resection can be safe and effective for HCC.

Functional Status

Patients with a ECOG Performance Score of 1–2 are considered to have "Advanced Stage" and thus are excluded from surgery within the BCLC. Despite this, in clinical practice PS may not be an absolute contraindication for hepatic resection (Wu et al. 2019; You et al. 2017; Zhong et al. 2014). Wu et al. showed that there was no difference in overall perioperative mortality and major morbidity among patients with PS-1 compared to PS-0 (Wu et al. 2019). Therefore, whilst surgical resection can be safe in higher PS, careful consideration must be undertaken in consultation with the patient and MDT setting. The patient outlined in the case above was a young male with no other significant comorbidities, with an excellent functional status.

Tumour Factors

Surgical resection can be considered in those classified as "very early stage" (BCLC 0) or "early stage" (BCLC-A) (Ettorre et al. 2017).

Very Early Stage (BCLC-0)

This stage is defined as a solitary HCC ≤2 cm without vascular invasion or extrahepatic spread, in fit patients with preserved liver function. Our case patient fits in this category, having a solitary segment 8 lesion of 2 cm.

The management of patients in this category depends on if they are a candidate for liver transplantation. Surgical resection allows pathological assessment of likelihood of early recurrence through the presence of adverse features such as microvascular invasion, poor differentiation or satellite disease. If a high risk of recurrence is detected within the specimen, liver transplantation may be considered (Fuks et al. 2012). Therefore, surgical resection should be first line for those who are potential transplantation candidates. Comparatively, if transplantation is not feasible, pathological assessment is less important, ablation should be favored over surgery, which obtains similar survival outcomes in this group (Cho et al. 2010; Cucchetti et al. 2013; Doyle et al. 2019; Izumi et al. 2019). If ablation is not possible, due to factors such as location or availability, or fails, surgical resection should be considered.

Early Stage (BCLC-A)

This group is defined as solitary HCC regardless of size or as a multifocal HCC with up to three nodules, each ≤3 cm, without macro vascular invasion or extrahepatic spread (as per Milan Criteria) (Mazzaferro et al. 1996). Additionally, the patient must have preserved liver function and fit. In those with solitary HCC, size of tumor itself does not necessarily impact the decision to proceed with surgery, so long as there is no vascular invasion or metastases. Rather, patient factors, such as those described earlier, come into play in determining resectability. Similar to BCLC-0, ablation can be considered for solitary lesions ≤2 cm with comparable survival (Citterio et al. 2016; Schnitzbauer 2017). However, for HCCs >3 cm, liver resection appears more cost-effective than ablation (Cucchetti et al. 2013). Solitary HCCs within BCLC-A stage that are unsuitable for resection due to patient factors but meet transplantation criteria should be considered for liver transplantation. Similarly, patients with BCLC-A stage multifocal HCC, should be recommended for liver transplantation rather than resection due to the higher risk of recurrence (N'Kontchou et al., 2009; Pompili et al. 2013; Reig et al. 2022; Shiina et al. 2012). If transplantation is not possible, the decision to proceed with surgery, ablation, or transarterial chemoembolization is debatable and should be individualized (Forner et al. 2015). Cohort studies of resection for multinodular HCC have reported reasonable survival rates (Bolondi et al. 2013; Fukami et al. 2020; Torzilli et al. 2013). Similarly, in a systematic review, Glantzounis et al. demonstrated a five-year survival of 49% in patients with ≤3 nodules. However more prospective data is required to fully evaluate its suitability in this cohort (Glantzounis et al. 2018).

Portal Vein Invasion

Patients with portal vein tumor thrombosis are considered to have advanced stage disease and thus exclude from curative treatments within the BCLC strategy. Some series have reported that liver resection for HCCs with portal vein invasion limited to first order branches offers longer survival than non-surgical treatments (Chirica et al. 2008; Kokudo et al. 2016, 2017; Pawlik et al. 2005; Pesi et al. 2015; Roayaie et al. 2013). A recent systematic review demonstrated reasonable five-year survival of 45% for those who underwent surgery and had distal port vein tumor thrombosis (Glantzounis et al. 2018). Nevertheless, a lack of prospective data precludes advocating for resection in this cohort as standard of care.

Underlying Liver Function and Future Liver Remnant

In addition to assessing the general health of patients with HCC being considered for hepatic resection, evaluating the severity of any underlying liver disease and future liver remnant is critical for determining the risk of and preventing postoperative liver failure and mortality. In well selected patients, operative mortality for HCC in patients with cirrhosis is low (Imamura et al. 2003).

Within previous modifications of the BCLC strategy, surgical candidates were those who were demonstrated to have "preserved liver function." This referred to patients with Child-Pugh A without ascites. Additionally, "optimal surgical candidates" were those who had compensated Child-Pugh A with a MELD score <10, minimal portal hypertension with acceptable future liver remnant (FLR) and the possibility to perform a laparoscopic approach (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018). The combination of these factors were suggested to lead to an expected mortality of <3% and morbidity of <20%, including a post-operative severe liver failure incidence of <5% (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018).

Whilst patients with Child-Pugh A are generally accepted as potential candidates for liver resection, surgery in those with Child-Pugh B cirrhosis must be considered carefully. Although not an absolute contraindication, in general, major hepatectomy should be avoided. Most surgical resections for HCC in Child-Pugh B should be limited to minor hepatectomy and use a minimally invasive approach in order to reduce morbidity (Kuroda et al. 2011; Troisi et al. 2021).

Clinically relevant portal hypertension (CRPH) is defined as a hepatic vein pressure gradient >10 mmHg. A recent meta-analysis examining the impact of CRPH on outcomes following hepatectomy for HCC demonstrated an increased the risk of three- and five-year mortality (pooled odds ratio [OR] for three-year mortality: 2.09; 95% confidence interval [CI]: 1.52–2.88; for five-year mortality: 2.07; 95% CI: 1.51–2.84) and the risk of postoperative clinical decompensation (pooled OR: 3.04; 95% CI: 2.02–4.59) (Berzigotti et al. 2015). That said, limited resection in those with preserved liver function and moderate portal hypertension has achieved reasonable outcomes (Citterio et al. 2016; Ishizawa et al. 2008; Ruzzenente et al. 2011; Santambrogio et al. 2013). Furthermore, laparoscopic approaches can help improve post-operative outcomes in select patients with CRPH (Ciria et al. 2016; Molina et al. 2018; Morise et al. 2015; Sposito et al. 2016; Witowski et al. 2019). Based on these results, recent guidelines do not consider CRPH to be a contraindication for minor hepatectomy (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018; Reig et al. 2022). Nevertheless, the decision to operate in these patients is dependent on numerous factors including extent of hepatectomy, severity of underlying liver dysfunction and availability of other therapeutic approaches such as ablative techniques and transplantation. Algorithms such as the one suggested by Citterio and colleagues can help predict the risk of decompensation post-operatively and select patients appropriately for resection (Figure 4) (Citterio et al. 2016).

In addition to using scoring systems like Child-Pugh score and presence of portal hypertension, assessment of liver function can be calculated using other parameters such as indocyanine green (ICG) kinetics, liver stiffness measurements (LSM) and scintigraphy (Cescon et al. 2012; De Gasperi et al. 2016; Makuuchi et al. 1993; Olthof et al. 2017). These techniques can also predict function of the future liver remnant (FLR), which is important to reduce post-operative morbidity and mortality from liver decompensation following hepatic resection (Itoh et al. 2017). In general, patients with normal liver function can tolerate an FLR of 20%, whilst those with cirrhosis are likely to need at least 40% to minimize the risk of liver failure following resection (Farges et al. 1999; Vauthey et al. 2000).

The degree of fibrosis in cirrhosis can be assessed using transient elastography by measuring liver stiffness. LSM above 12–14 kPa is associated with a significant risk of post-operative liver failure (Llop et al. 2012; Wong et al. 2013). Further, LSM can also be used to estimate safe FLR (Nishio et al. 2016). Similarly scintigraphy using either technetium 99m-labeled mebrofenin or diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (99 mTc-GSA) can be used to measure both volume and function of the FLR and predict when surgical resection can be undertaken safely (Okabayashi et al. 2017; Olthof et al. 2017).

Although these techniques are useful, ICG kinetics and hepatobiliary scintigraphy are not widely available. Three-dimensional volumetric analysis using contrast-enhanced computed tomography can be used to measure total liver volume as well as volume of the FLR (Simpson et al. 2014; Yamanaka et al. 2007). Additionally, magnetic resonance imaging using a hepatocyte-specific contrast agent (Gd-EOB-DTPA) can give anatomical and quantitative information regarding the function of the FLR and predict post-operative liver failure (Chuang et al. 2018).

How Can We Optimize the Future Liver Remnant Pre-operatively?

If pre-operative assessment of FLR in an otherwise appropriate surgical candidate is demonstrated to be inadequate there are several strategies available to induce hypertrophy of the FLR. The most common of these is portal vein embolization (PVE) of the involved lobe/segments, which results in increased flow to the unaffected liver stimulating cytokine and growth factor release. This results in hypertrophy of the FLR, which can range between 25–50% within 4–6 weeks (Abulkhir et al. 2008; Aoki and Kubota 2016; Chuang et al. 2018; Huang and Aloia 2017). As a result, PVE has been shown to reduce post-operative liver failure and mortality following major hepatectomy (Farges et al. 2003; Shindoh et al. 2012). That said, there are reports of increased tumor growth following PVE (Hoekstra et al. 2012). The possible mechanism for this could be due to the increase in hepatic arterial flow to the diseased liver following PVE (Aoki and Kubota 2016).

There are some other options available to increase FLR in patients with insufficient reserve function. Recently, the addition of hepatic vein embolization to PVE has been demonstrated to be safe and effective at further increasing liver hypertrophy (ranging from 33–63% growth) prior to resection in patients initially deemed to have insufficient FLR, although

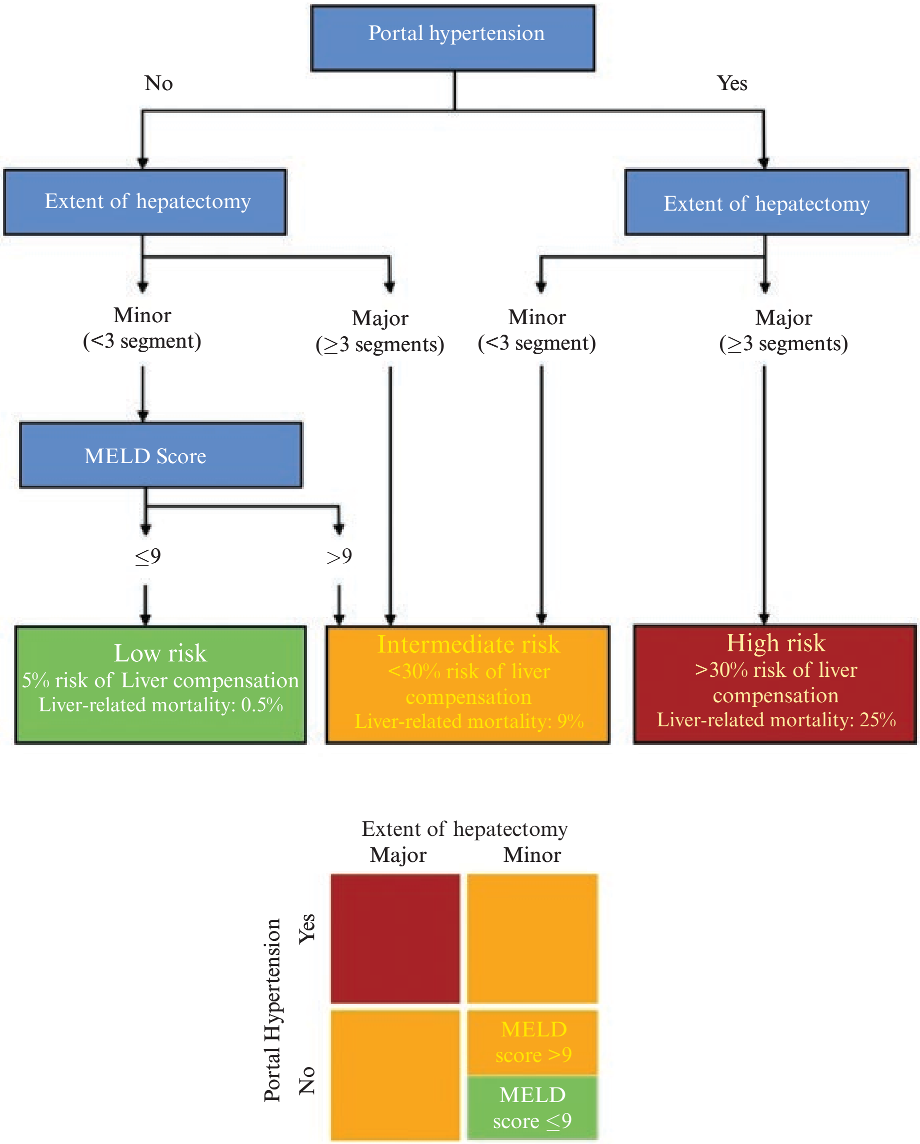
Portal hypertension
No
Yes
Extent of hepatectomy
Extent of hepatectomy
Minor (<3 segment)
Major (≥3 segments)
Minor (<3 segment)
Major (≥3 segments)
MELD Score
≤9
>9
Low risk
5% risk of Liver compensation
Liver-related mortality: 0.5%
Intermediate risk
<30% risk of liver compensation
Liver-related mortality: 9%
High risk
>30% risk of liver compensation
Liver-related mortality: 25%
Extent of hepatectomy
Major
Minor
Portal Hypertension
Yes
No
MELD score >9
MELD score ≤9

Figure 4 Assessment of the risk of liver decompensation and mortality following liver resection for HCC in portal hypertension and cirrhosis. Stratification into high (red), intermediate (yellow), and low (green) risk of liver decompensation depending on portal hypertension, extent of resection and liver function. Adapted from Citterio et al. (2016).

further work is needed in its use in patients with cirrhosis (Esposito et al. 2019). Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) is another strategy that has been shown to induce rapid hypertrophy in the remnant liver in those with inadequate pre-operative FLR (Oldhafer et al. 2016). This involves a two-staged hepatectomy with surgical ligation of the portal vein branch supplying the lobe or segments involved with HCC and parenchymal transection during the first stage, followed by completion hepatectomy after 1–2 weeks. Whilst ALPPS can be used as alternative to PVE or as a salvage procedure following insufficient hypertrophy after PVE, mortality rates appear to be higher than PVE (Schnitzbauer 2017).

What Surgical Factors Need to Be Considered?

Anatomical vs Non-anatomical Liver Resection

The extent of liver resection should be defined based on international terminology (Strasberg 2005). Anatomical resection involves parenchymal transection along planes of liver segments delineated by Couinaud and selective ligation of the inflow portal triad and outflow hepatic veins to these segments. From an oncological viewpoint, anatomical resection is considered the surgical approach of choice due to the propensity for vascular invasion of segmental portal veins and to include surrounding satellite lesions (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018). That said, non-anatomical resection can be considered when preservation of liver parenchyma is paramount to prevent post-operative decompensation, such as patients with borderline FLR.

Minimally Invasive vs Open Liver Resection

The safety, feasibility and efficacy minimally invasive liver resection for select patients with HCC in experienced centers has been demonstrated in several meta-analyses. Minimally invasive techniques may have an advantage over open surgery for those with cirrhosis and portal hypertension (Troisi et al. 2021).

Liver Transplantation

Liver transplantation (LTx) for unresectable hepatocellular carcinoma (HCC) was considered as an attractive option in early days of liver transplantation. However, initial experiences proved to be very unsatisfactory due to the frequent recurrence of the tumor and poor outcomes (Iwatsuki et al. 1985). The milestone study by Mazzaferro et al., published in 1996, implemented a clearly defined selection criteria for LTx, has started a new chapter in this area (Mazzaferro et al. 1996). This Milan criteria stood the test of the time as a point of reference despite being modified, expanded or refined.

According to the most recently updated European Liver Transplant Registry, patients with HCC comprise an estimated 20% of all transplant patients between the age of 45–60 years. LTx patients older than 60 years represent approximately 31% of all transplant cases (http://www.eltr.org). Even with progress and improved overall survival for patients with HCC who underwent LTx, several challenges remain. Various aspects of liver transplant assessment, bridging and downstaging therapies, organ allocation, and tumor recurrence following LTx have highlighted the problems that need to be addressed.

Selection Criteria

A landmark study by Mazzaferro published almost three decades ago played a critical role in establishing LTx as an effective modality in the treatment of HCC in patients with liver cirrhosis (Mazzaferro et al. 1996). It demonstrated that in patients with a single lesion with the diameter ≤ 5 cm or up to three lesions with the diameter ≤ 3 cm, with the absence of vascular invasion and metastatic spread, four-year survival was 75% with a low recurrence rate of 15%. This study set a scene for further developments in the area of LTx for HCC. Over time, these criteria have been challenged as being too restrictive precluding LTx in a significant proportion of patients who could potentially benefit from this procedure. As a result, the University of California, San Francisco (UCSF), has introduced a new criteria, frequently called the UCSF criteria (Yao et al. 2001). According to these criteria, LTx could be considered if the patients have a single lesion with a diameter of ≥6.5 cm, or ≤3 lesions with the largest lesion consisting of a diameter of ≤4.5 cm. The total diameters of all lesions should be ≤8 cm. Patient prognosis with the UCSF criteria was similar to the Milan criteria (Yao et al. 2007).

Tumour histology has been postulated as a criterion for LTx by the University of Toronto, where the size of the tumor does not play a critical role in selecting a patient for LTx provided the lesion is not histologically poorly defined and there are no extrahepatic metastases. These so called Extended Toronto (ETC) criteria offer a five-year survival of 68% which is not statistically different from the Milan criteria. Nevertheless applying these criteria is associated with higher recurrence rate (Sapisochin et al. 2016). Another criteria were postulated by Toso et al. and combined the tumor size and levels of alpha-fetoprotein (AFP) (Toso et al. 2015). Under these criteria, patients were referred for LTx if the total tumor volume was ≤115 cm^3 and AFP level was ≤400 ng/ml.

Despite the newer revised measures, the Milan criteria remained as the primary standard for the patients selection for LTx and a reference for comparison with other criteria (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018). According to the European Association of for the Study of the Liver Clinical Practice Guidelines, there is no consensus as to the universal application of extended criteria (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018). Patients who exceed the Milan criteria can be considered as transplant candidates following effective downstaging procedures, which decrease the size of the tumor to the limits set by the criteria. Vascular invasion of the tumor at the portal or hepatic vein, and the presence of extrahepatic metastases remain as definitive contraindications for LTx. Nevertheless, it is worthwhile to mention that vascular invasion is not an absolute contraindications in the context of living related donor liver transplantation (LDLT) (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018). In Asia, a donation process in LDLT is considered as being a personal gift decreasing the demand on cadaveric donor LTx. As many as 30–40% of LDLT performed over there are done for very advanced tumors exceeding the Milan criteria (Lee et al. 2017).

Marginal cadaveric donor livers can be used in patients with HCC. However, currently there are no guidelines to regulate the allocation of marginal livers for patients with and without HCC. Criteria for prioritization should take into account features such as the tumor size, biology, and the expected time on the waiting list (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018).

Downstaging Therapy

Downstaging in HCC is defined as treatment aimed at reducing the tumor mass to meet the standard sizes indicated in the Milan criteria. The American Associated for the Study of Liver

Disease (AASLD) guidelines for the treatment of HCC suggest LTx in patients who underwent a successful downstaging to meet Milan criteria (Heimbach et al. 2018) (Figure 5). These procedures proved successful in reducing recurrence rate and prolonging survival (Jang et al. 2010; Ravaioli et al. 2008).

Most frequently used treatment modalities for downstaging include transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). According to a recent meta-analysis, successful downstaging can be achieved in about 50% of patients, no matter which modality was used. Significantly, a high rate of efficacy for downstaging, nearly 60%, can be obtained with a combined TACE and RFA therapeutic approach (Cescon et al. 2013). In fact, a lack of accepted response to downstaging may suggest more aggressive biology of the tumor (Cescon et al. 2013). Most recent study from Milan analyzed the outcome of liver transplantation in subjects who underwent a downstaging of the tumor mass, which exceeded their own Milan criteria (Mazzaferro et al. 2020). The study was open-labeled and randomized. Inclusion criteria comprised of tumor size exceeding the Milan criteria, absence of microvascular invasion or metastases, and a stable liver function with a Child-Pugh score of up to 7 points. TACE or a combined therapeutic approach was used for downstaging procedures. Following a successful downstaging process, patients were randomized into transplantation and control groups. The event-free five-year survival was 77% versus only 18% in the control group confirming the effectiveness of this approach.

Organ Allocation to Patients with Liver Cirrhosis and HCC

The scarcity of donor livers requires the necessity for the implementation of a fair system of organ allocation. Model of End-Stage Liver Disease (MELD) scoring which was updated with the measurement of serum sodium levels (MELD-Na) plays a

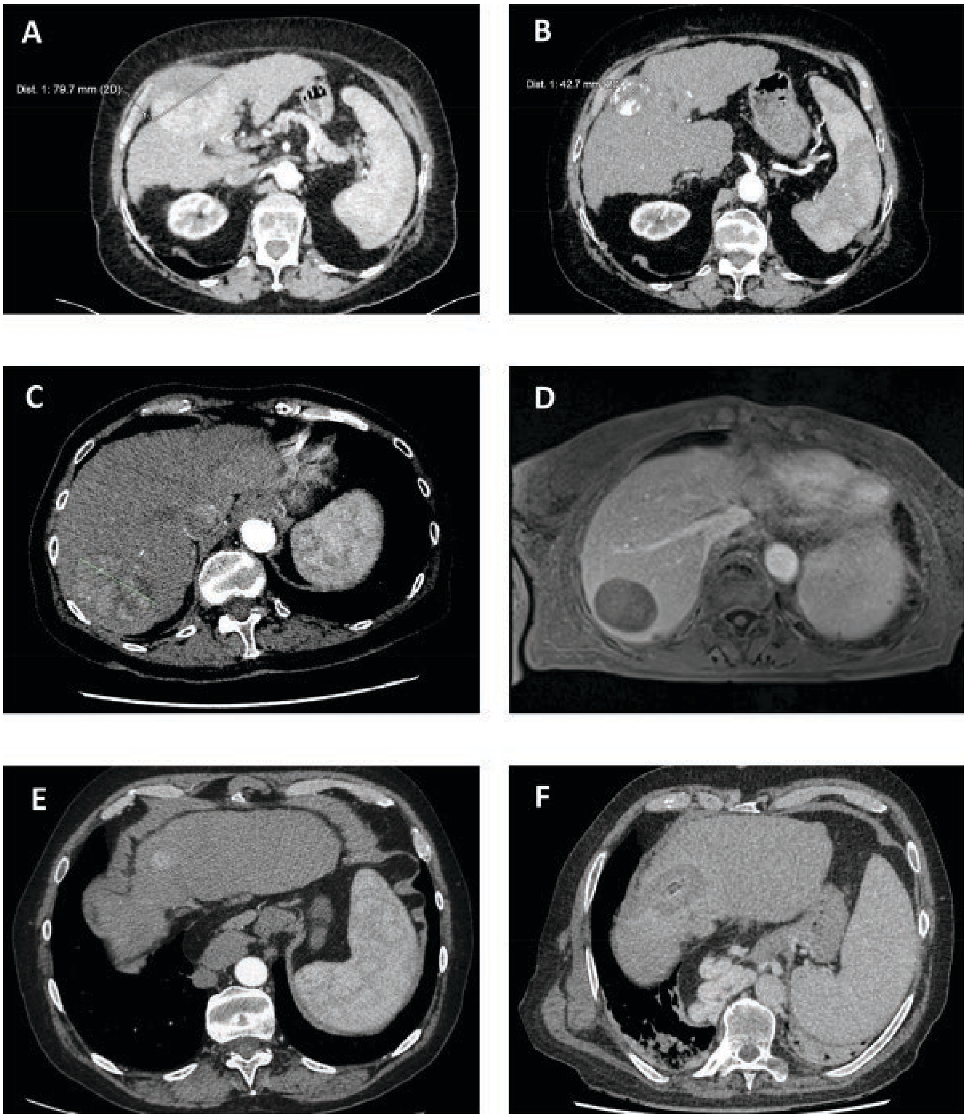

Figure 5 Downstaging with TACE (A–D) procedures in two patients exceeding Milan criteria. A, C before the procedure; B, D after the procedure. A, B and C show CT images; D shows MRI image. E–F downstaging with RFA; E – before the procedure; F after the procedure. Pictures courtesy of Dr K. Korzeniowski and Dr G. Rosiak.

crucial role in distribution of organs for orthotopic LTx across various indications. MELD has been proven in various studies to be currently the most decent index determining the placement of patients with end stage liver disease on the transplant waiting list. Nevertheless, MELD index, designed for end stage cirrhosis, fails to be a reliable modality for organ allocation in cirrhotic patients diagnosed with HCC.

Many patients with HCC remain clinically stable with well-preserved liver function. Automatic adoption of MELD measurements would make them very unlikely to receive their transplants on time. This is due to high risk of tumor progression, which may potentially exceed accepted criteria, resulting in the removal of the HCC patients from the waiting list. Thus, additional points are added for subjects with HCC to increase their opportunity for transplantation. They are called MELD exception points. Different systems are applied in various countries. There has been an evolution of this idea over last 20 years, with the allocation of livers to patients with HCC in United States being a good example of this issue. Back in 2002, patients with HCC received 29 exception points for T2 HCC lesions which was lowered to 22 points in 2005. In order to avoid transplanting aggressive or advanced HCC, a new "six-month" rule was introduced in 2015. According to this policy, patients with cirrhosis and T2 HCC are initially listed with their calculated MELD-Na score and usually submitted to interventional radiology bridging therapy. After a six-month period, such patients receive a MELD exception score of 28 points provided they still remain within Milan criteria with an AFP level of <1000 ng/ml. Those who exceeded the Milan criteria and/or have an AFP of >1000 ng/ml, must not be placed on the waiting list and often undergo a trial of neoadjuvant downstaging therapy like TACE or RFA. Patients eligible for downstaging are those with one lesion > 5 cm in diameter (but ≤ 8 cm) or 2–3 lesions each > 3 cm but < 5 cm in diameter (but total diameter of all lesions ≤ 8 cm) or 4–5 lesions each < 3 cm (but total diameter of all lesions ≤ 8 cm). Only if HCC becomes downstaged to stay within the Milan criteria and AFP level drops below 500 ng/ml, they can be placed on the waiting list receiving exceptional MELD score. Their points increase by 10% every three months with a maximum of 34 points. In Europe, each country has its own criteria for MELD exception points for HCC patients. For example, in the Eurotransplant Zone, patients with HCC receive 20 or 22 points at inclusion on the list depending on the country. The number of points is increased by 10% every three months after being placed on the waiting list.

Bridging Therapy

Since waiting time for LTx remains unpredictable, implementation of neoadjuvant procedures with the aim of reducing the tumor size remains as a significant treatment approach. Indeed, despite the scarcity of solid data coming from properly designed, randomized studies, the EASL Guidelines (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018) recommend this therapeutic strategy to reduce the patient dropout rate from the transplant list, which is estimated to be 10–20% (Majno et al. 2011; Yao et al. 2003). Also AASLD Guidelines recommend neoadjuvant therapy in all patients on the transplant list who fulfill the Milan criteria; however, they do not recommend any particular treatment approach (Heimbach et al. 2018).

TACE, RFA, percutaneous ethanol injections (PEI), microwave ablation, and radio embolization are the principal modalities for neoadjuvant therapy. A conclusive treatment approach has not been established due to current data being only from short series studies and the lack of proper randomized research. Another approach was investigated for patients with small tumors. These patients underwent surgical resection of their lesions and then received LTx. Unfortunately, the results of the study was disappointing (Adam et al. 2003) showing worse five-year survival and increased HCC recurrence when compared to patients who were directly scheduled for LTx.

The role of AFP levels during the waiting period on the transplant list has been reinforced in a study involving 1450 patients with HCC, including 235 who exceeded the Milan criteria (Halazun et al. 2018). The results indicated that subjects with an AFP level consistently <200 ng/ml showed the most favorable outcome. These authors introduced a new prognostic model called the New York/California (NYCA) score, which incorporated AFP level. This criterion allowed the transfer of 85% of patients who did not meet the Milan criteria into the low/acceptable risk group.

Tumor Recurrence and Prognosis

Expected five-year survival rate for patients transplanted within the Milan criteria are estimated to be between 65% and 80% (EASL clinical practice guidelines: management of hepatocellular carcinoma 2018), indicating a significant survival benefit when compared to transplants done in patients exceeding the criteria (Clavien et al. 2012). Recurrence of HCC after LTx has been seen in around 8–20% of transplant (Santopaolo et al. 2019), and the tumors are extrahepatic in a significant proportion of patients. There is a risk increase with more liberal criteria as confirmed with the multicentre study (Mazzaferro et al. 2009). Factors such as the size and number of lesions, AFP levels, and inflammation index (neutrophil/lymphocyte ratio) all play their role (Halazun et al. 2009). Morphological features of the tumor were analyzed in explanted livers to determine their prognostic value. These factors include tumor micro- and macro-vascular invasion, presence of satellite lesions, and tumor differentiation grade. As in vast majority of cases the diagnosis is established on imaging such as CT or MRI the knowledge on these features are of little practical value.

In 2017, a scoring system was suggested to be applied in patients fulfilling the Milan criteria. The Risk Estimation for Tumor Recurrence After Transplant (RETREAT) is composed of three features that are independently related to the increased risk of recurrence (Mehta et al. 2017). These include:

a Microvascular invasion:
  a 0 points if not present
  b 2 points if present
b Serum AFP level at LTx:
  a 0 points if 0–20 ng/ml
  b 1 point if 21–99 ng/ml
  c 2 points if 100–999 ng/ml
  d 3 points if >1000 ng/nl
c Diameter of the largest lesion/number of lesions
  a 0 to 3 points depending on the total number of lesions (way of point calculation in (Mehta et al. 2017)).

For example, the risk of recurrence in patients who scores five points in total is estimated to be 75%.

Overall survival in patients transplanted for HCC can be calculated from a simple scoring system available at http://www.hcc-olt-metroticket.org This project was endorsed by the European Liver and Intestine Transplant Association (ELITA) and the International Liver Transplantation Society (ILTS). It was based on a study on more than 1000 liver transplants for HCC in patients exceeding the Milan criteria. It considers the size of the largest tumor, number of lesions, and the serum level of AFP. The latter is an indicator of a poor prognosis. For example, in a hypothetical patient with one lesion of 3 cm in a diameter and a AFP level of 5 ng/ml, the five-year predicted survival rate is 94% However, in another hypothetical patient with the same tumor size but an AFP level of 1000 ng/ml, the five-year survival significantly decreases to 67%. Some authors also link the risk of recurrence of HCC after LTx with high levels of immunosuppressive agents, such as calcineurin inhibitors (CNIs) (Vivarelli et al. 2005). Nevertheless, these data require confirmation in larger studies.

Prevention of HCC Recurrence

Immunosuppressive agents, such as sirolimus or everolimus, are increasingly used in the post-transplant setting and have shown to reduce the proliferative activity of HCC. Both drugs are inhibitors of mammalian target of rapamycin (mTOR) pathway. mTOR inhibitors may inhibit growth and metastatic spread of HCC (Dawson 2011; Shanker et al. 2021). A meta-analysis encompassing five publications, which included 474 patients, demonstrated a lower recurrence rate, significantly better recurrence-free survival, and a decreased rate of mortality in patients treated with mTOR inhibitors compared to CNIs (Shanker et al. 2021). Nevertheless, a subsequent multicenter, randomized controlled study in patients transplanted for HCC with the mTOR inhibitor sirolimus did not show a similar benefit of this agent. The five-year recurrence-free survival did not improve significantly when compared to immunosuppression protocols, including CNIs. Therefore, the efficacy of mTOR inhibitors in the context of LTx in HCC patients remains controversial.

How about the Role of Radiotherapy?

Case: A 55-year old fit male with eradicated Hepatitis C and Child-Pugh A5 cirrhosis, developed a solitary 2 cm lesion in segment 6 on surveillance imaging, with an elevated AFP. CT and MRI were characteristic for HCC. Significant portal hypertension precluded surgery, and the MDT recommended TACE. Two years later he developed local only recurrence (Figure 6a, b). Liver transplant was recommended if the recurrence could not be controlled with local therapy. The lesion did not respond to a second TACE, and attempts at MWA were aborted after recurrent iatrogenic pneumothoraces. The MDT recommended stereotactic body radiotherapy (SBRT) and the patient received 50 Gy in five treatments over two weeks. He experienced transient grade 1 back pain after fraction 1, and developed no other significant acute or sub-acute toxicities. A CT at three months showed no evidence of residual HCC with a normalized AFP.

What Is the Role of SBRT in the Management of HCC?

Recent data and preliminary results from current studies highlight the increasingly important role of RT as a key treatment modality for HCC. HCC is a radiosensitive tumor, and with growing evidence, stereotactic body radiation therapy (SBRT) is emerging as an effective alternative where first-line modalities are unsuitable. The range of patients suitable for focal irradiation extends from very early to advanced/palliative stages, as demonstrated in Figure 7 (Dawson 2011).

SBRT is modern external beam radiation therapy which delivers an intense dose of radiation to treatment targets with high accuracy over a small number of treatments (fractions, #). Radiation therapy (RT) can target lesions unsuitable for TACE due to macro vascular invasion (MVI), or challenging tumor arterial supply, and lesions where size or location (e.g. subdiaphragmatic) may limit ablative therapies (Dawson 2011).

For patients with HCC, SBRT achieves sustained local control (LC) with lower risks of radiation-induced liver toxicities compared to historical external beam radiotherapy (EBRT) (Shanker et al. 2021). Through increasing awareness of liver tolerance to RT and interactions with prior therapy, reducing low-moderate doses to normal liver, and using modern RT techniques, the risk of radiation-induced liver disease can be minimized. A recent systematic review and meta-analysis of 49 prospective and retrospective SBRT studies reported pooled 1- and 3-year LC rates of

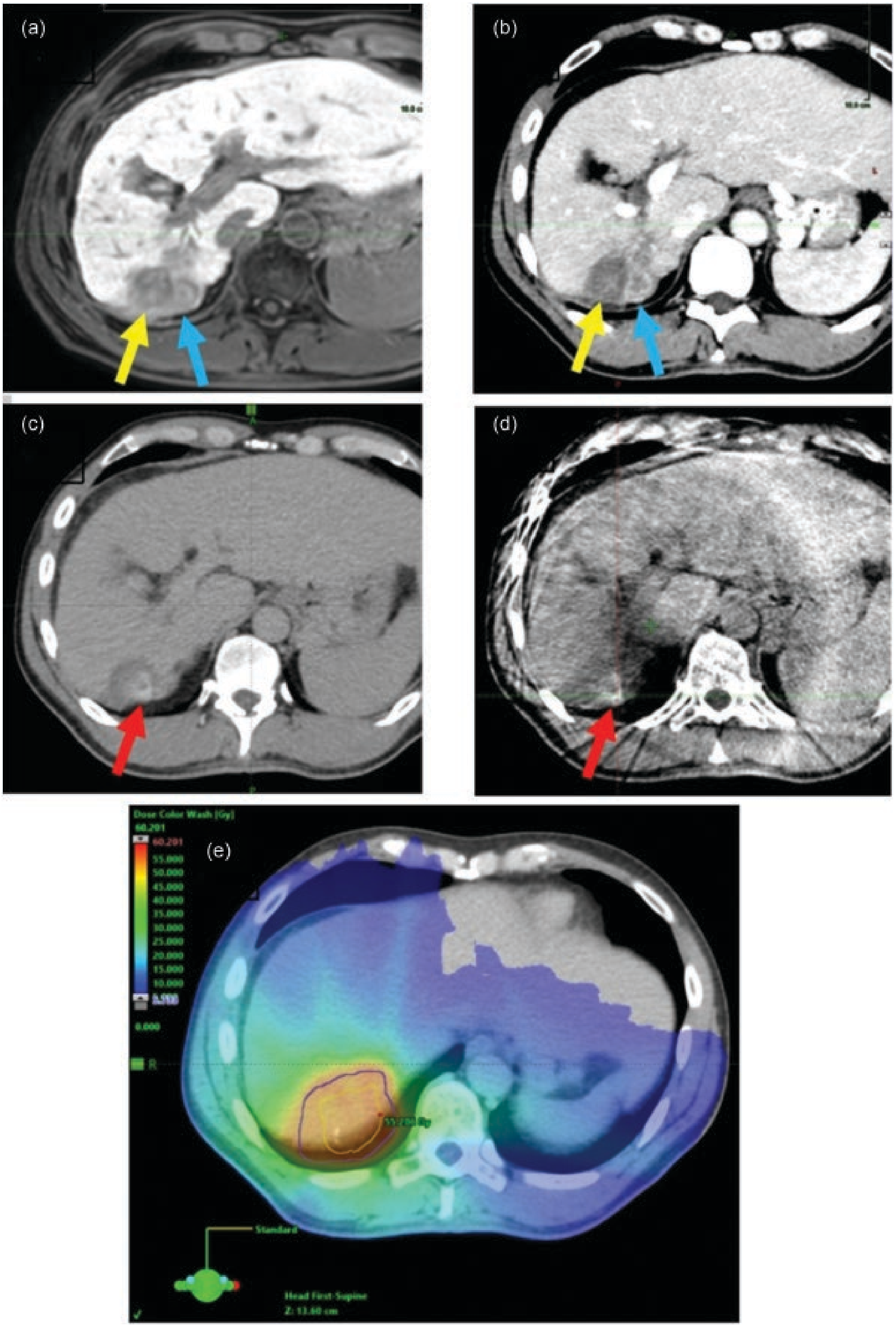
(a)
(b)
(c)
(d)
(e)
Dose Color Wash [Gy]
60.201
60.201
55.000
50.000
45.000
40.000
35.000
30.000
25.000
20.000
15.000
10.000
0.000
R
Standard
Head First-Supine
Z: 13.60 cm

Figure 6 Representative axial images of SBRT treatment planning and delivery for our case a,b) Fused MRI planning scan with Primovist™ (a), and CT planning scan with contrast for SBRT (b), demonstrating gross tumor (GTV, blue arrow), and prior TACE/MWA treatment changes (yellow arrow) c,d) non-contrast planning CT (c), and cone beam CT acquired at the time of SBRT for image guidance/verification (d), demonstrating hypodense TACE/MWA cavity and hyperdense residual lipiodol staining (red arrow). e) Dose color wash of SBRT plan, with treatment prescription (50Gy) in red color wash encompassing planning target volume (PTV, purple line = GTV (yellow line) + margin for tumor motion and setup error) with steep dose drop-off into surrounding liver.

91.1% and 84.2% respectively. The pooled 1- and 3-year overall survival (OS) rates were 78.4% and 48.3%, and SBRT was associated with acceptable rates of toxicity (median grade 3 rate 6.5%) (Shanker et al. 2021).

The role of RT (using proton beam therapy) for recurrent small inoperable HCC (<3 cm, ≤2 lesions) was established by a contemporary randomized phase III study, which reported a 94.8% two-year local progression free survival (LPFS) rate, which was non-inferior to RFA (LPFS 83.9%) (Kim et al. 2021).

Local control appears to decline with increasing lesion size, however large and advanced stage tumors (>5 cm and/or MVI) remain associated with very acceptable local control rates with SBRT (82% and 67% at 1- and 3-years respectively) (Shanker et al. 2021, 2021).

For liver-confined HCC with MVI, RT can be sequenced with catheter-based or systemic therapies for vascular recanalization and sustained tumor control (Apisarnthanarax et al. 2022). In a retrospective review of 557 patients with MVI treated with TACE, TACE plus RT, or Sorafenib, it was found TACE plus RT was associated with longest duration of PFS and OS (Kim et al. 2015). A subsequent randomized prospective study demonstrated a significantly longer time to progression and improved OS with TACE plus RT compared with Sorafenib in treatment-naive HCC patients with MVI (Yoon et al. 2018). Of the patients in the TACE-RT arm, 11.1% proceeded to curative surgical resection.[7] It is recognized that RT in this trial (Yoon et al. 2018) was not SBRT, and sorafenib is no longer the standard of care for systemic therapy (discussed previously), and so contemporary trials for advanced stage disease are awaited (Table 5). Recommendations for RT in the neoadjuvant setting prior to surgical resection or orthotopic liver transplant with/without MVI are based on low level evidence (Apisarnthanarax et al. 2022).

At the time of writing, there are over 45 trials with status recruiting, not yet recruiting, or active (not currently recruiting), listed on clinicaltrials.gov which involve SBRT for HCC including comparisons and/or combinations of RT with other local and systemic therapies. Table A includes 9 highly anticipated phase III trials investigating SBRT in the management of HCC.

As emerging literature continues to highlight the role of RT as an essential modality in the management of HCC, it is anticipated that multidisciplinary approaches and therapeutic guidelines will evolve accordingly.

Systemic Therapy

Case: A 65 year old male has a history of Child-Pugh A cirrhosis from chronic Hepatitis B infection and alcoholic liver disease, complicated by HCC. He initially had a segmental liver resection of a 37 mm moderately poorly differentiated HCC lesion with clear margins. However, he progressed aggressively a few months later, developing multifocal HCC (Figure 8) with portal vein invasion (Figure 9), and an associated elevated AFP to 22500. After discussion at an MDT, he was commenced on systemic treatment (first-line immunotherapy – atezoluzimab and bevacizumab). His pre-treatment gastroscopy showed grade 1 esophageal varices with portal hypertensive gastropathy.

Who Do We Consider for Systemic Therapy?

Systemic treatment is indicated in BCLC Stage C which includes HCC cases with vascular invasion or metastatic spread (with lymph node involvement or distant metastases) in patients with preserved liver function (Child-Pugh A–B) with an ECOG performance status of 1–2. It also should be considered in patients with non-resectable HCC (either due to extent of disease, tumor location, poor functional status or significant comorbidities) where either locoregional therapies have failed to control disease or cannot be delivered (due to risk of upending remaining liver function). Our case patient fits into this category recurrence to multifocal HCC with portal vein invasion, with reasonable functional status.

What Factors Should We Consider Prior to Systemic Therapy?

Many patients with HCC will have underlying HBV and HCV infection, and will be at risk for viral reactivation during active immunotherapy. Guidelines (ASCO) suggest HBV screening for all patients in this category. Patients who have either chronic HBV infection or past HBV infection require a reactivation risk assessment to confirm if antiviral prophylaxis is needed (Hwang et al. 2020; Pinter et al. 2021).

VEG-F inhibitors, including bevacizumab, are associated with a higher risk of bleeding complications. Patients must be evaluated for the presence of varices and have them treated as indicated within six months prior to initiating immunotherapy. After variceal ligation, treatment should be delayed for 14 days minimum, given the risk of post-banding ulceration bleed is highest within 10 days. This treatment should be avoided in patients with untreated high-risk varices, or active bleeding. This is why our case patient had a pre-treatment gastroscopy which did, in fact, show grade 1 esophageal varices with portal hypertensive gastropathy.

Immunotherapy is contraindicated in solid organ transplant recipients where organ rejection may be life-threatening or when organ replacement therapy is not available, and therefore, should not be considered in HCC patients who recur following liver transplantation. TKIs and anti-VEGF antibodies can be considered in place of anti-PD-1/PDL-1/CTLA-4 therapies in recurrent HCC post transplant.

Patients with HCC may suffer from hepatobiliary autoimmune diseases such as AIH, PBC, and PSC (Sangro et al. 2021).

Table 5 The emerging role of SBRT in the management of HCC; Phase III trials with status recruiting, not yet recruiting or active (not currently recruiting) on clinicaltrials.gov.

Trial name/identifier	Study arms	Primary outcome measures
Transarterial Chemoembolization (TACE) Versus TACE Plus Stereotactic Body Radiation Therapy (SBRT) in Liver Carcinoma (TACE) NCT03895359	Arm A: TACE Arm B: TACE + SBRT	1. Overall Survival at 2 years 2. Time to Intrahepatic Progression
Stereotactic Body Radiation Therapy (SBRT) Versus Trans-Arterial Chemoembolization (TACE) as Bridge to Liver Transplant NCT03960008	Arm A: SBRT Arm B: TACE (Drug – Doxorubicin)	Duration of disease control (1 year post-treatment)
SBRT or TACE for Advanced HCC NCT03338647	Arm A: TACE with drug eluted beads or doxorubicin/lipiodol Arm B: SBRT with risk adapted dose prescription	Progression (total of local, intra- and extrahepatic) at 1 year
Sorafenib Tosylate with or Without Stereotactic Body Radiation Therapy Patients with Liver Cancer NCT01730937	Arm A: Sorafenib tosylate Arm B: SBRT followed by Sorafenib tosylate	Overall survival
Transarterial Chemoembolization Compared with Stereotactic Body Radiation Therapy or Stereotactic Ablative Radiation Therapy in Treating Patients with Residual or Recurrent Liver Cancer Undergone Initial Transarterial Chemoembolization NCT02762266	Arm A: TACE Arm B: SBRT	Median time to freedom from local progression (FFLP) up to 12 months
SBRT+TACE+Sorafenib Vs Sorafenib in the Treatment of uHCC with PVTT NCT04387695	Arm A: SBRT+TACE +Sorafenib (SBRT first for the PVTT +TACE for HCC, followed by sorafenib) Arm B: Sorafenib	Progression-free survival (PFS) rate at 12 weeks after randomization
Combination of Sintilimab and Stereotactic Body Radiation Therapy in Hepatocellular Carcinoma (ISBRT01) NCT04167293	Arm A: SBRT + PD-1 Arm SBRT followed by sintilimab (within 4–6 weeks) Arm B: SBRT alone	24-week progression-free survival (PFS) rate
RFA vs. SBRT for Small HCC NCT03898921	Arm A: Stereotactic Body Radiotherapy (SBRT) Arm B: Radiofrequency Ablation (RFA) (no more than 3 procedures)	3-year overall survival rate
TACE vs TACE+SBRT for Unresectable Hepatocellular Cancer (TACE-SBRT) NCT02794337	Arm A: DEB-TACE (max 3 with 12 months Sorafenib) Arm B: DEB-TACE+SBRT arm (TACE as per arm A, SBRT 4–6 weeks after TACE with 12 months Sorafenib)	In-field Progression Free Survival up to 24 months

Current guidelines suggest that immunotherapy should be avoided when autoimmune disease reactivation may be life-threatening (for example, in neurological or neuromuscular disorders) and in patients with poorly controlled autoimmune disease or those requiring high dose immunosuppression for control. In these patients, TKIs should be considered in preference to immunotherapy (Sangro et al. 2021).

VEG-F inhibitors are generally contraindicated in patients with severe cardiovascular diseases, or a history or risk of life-threatening or significant thrombotic or bleeding events (bleeding diathesis or significant coagulopathy), serious/dehiscing/active non-healing wounds, or poorly controlled hypertension (Finn et al. 2020). Patients should also not be in need of full-dose anticoagulation or anti-platelets. VEG-F inhibitors are also associated with nephrotoxicity, most commonly proteinuria. Before initiating therapy with bevacizumab, patients with pre-existing conditions such as diabetes, hypertension, or chronic kidney diseases should be screened for baseline proteinuria.

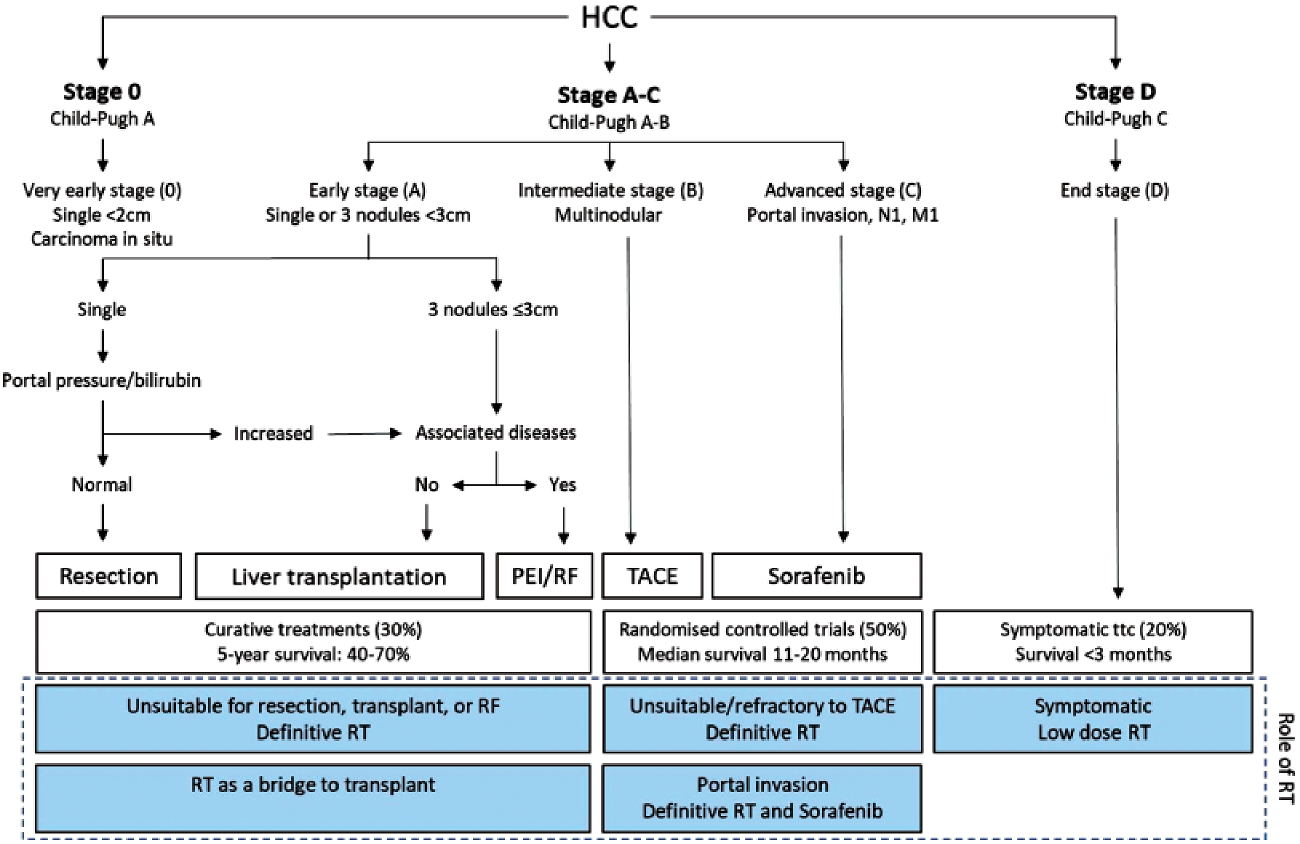
HCC
Stage 0
Child-Pugh A
Stage A-C
Child-Pugh A-B
Stage D
Child-Pugh C
Very early stage (0)
Single <2cm
Carcinoma in situ
Early stage (A)
Single or 3 nodules <3cm
Intermediate stage (B)
Multinodular
Advanced stage (C)
Portal invasion, N1, M1
End stage (D)
Single
3 nodules ≤3cm
Portal pressure/bilirubin
Increased
Associated diseases
Normal
No
Yes
Resection
Liver transplantation
PEI/RF
TACE
Sorafenib
Curative treatments (30%)
5-year survival: 40-70%
Randomised controlled trials (50%)
Median survival 11-20 months
Symptomatic ttc (20%)
Survival <3 months
Unsuitable for resection, transplant, or RF
Definitive RT
Unsuitable/refractory to TACE
Definitive RT
Symptomatic
Low dose RT
RT as a bridge to transplant
Portal invasion
Definitive RT and Sorafenib
Role of RT

Figure 7 Barcelona Clinic Liver Cancer (BCLC) classification for HCC including estimated incidence and accepted therapeutic options, including potential roles for RT as shown in the blue boxes. (Adapted from: *Overview: Where Does Radiation Therapy Fit in the Spectrum of Liver Cancer Local-Regional Therapies*) (Shanker et al. 2021).

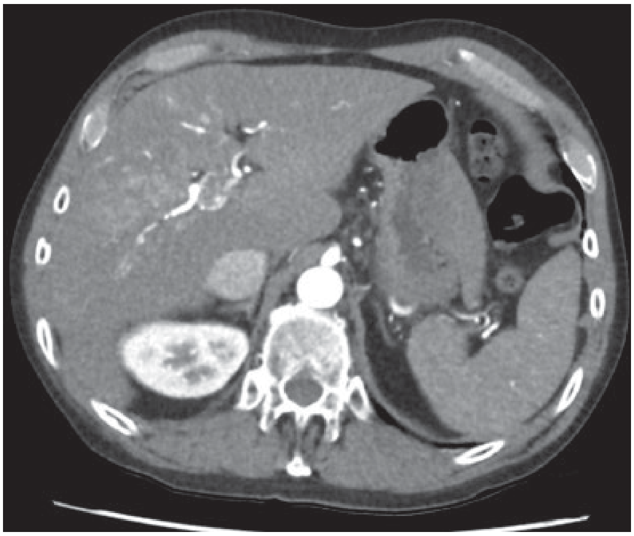

Figure 8 Multiple areas of arterial enhancement suggestive of multifocal HCC (courtesy of Radiology Department, St George Hospital Australia).

Is There One Etiology of HCC that Responds Better to Immunotherapy?

Emerging data suggest that immunotherapy might be less effective for NASH-related HCC compared with other etiologies. When data across 1656 patients from three key trials (Finn et al. 2020; Pfister et al. 2021; Yau et al. 2022) were stratified according to underlying etiology of chronic liver disease, survival benefit of PD-1 and PDL-1 targeted immunotherapy was reduced in those with NASH compared with other causes (7.1 months vs 14.4 months). This has been thought to be related to the aberrant T-cell activation that occurs in NASH leading to impaired immune surveillance. Despite this, based on the current data, it is not yet recommended in clinical guidelines to consider this in the decision of treating with immunotherapy (Gordan et al. 2020).

First-line Systemic Therapy

Immunotherapy (Atezolizumab and Bevacizumab)

The combination of atezolizumab (programmed death-ligand 1 antibody) and bevacizumab (anti-vascular endothelial growth

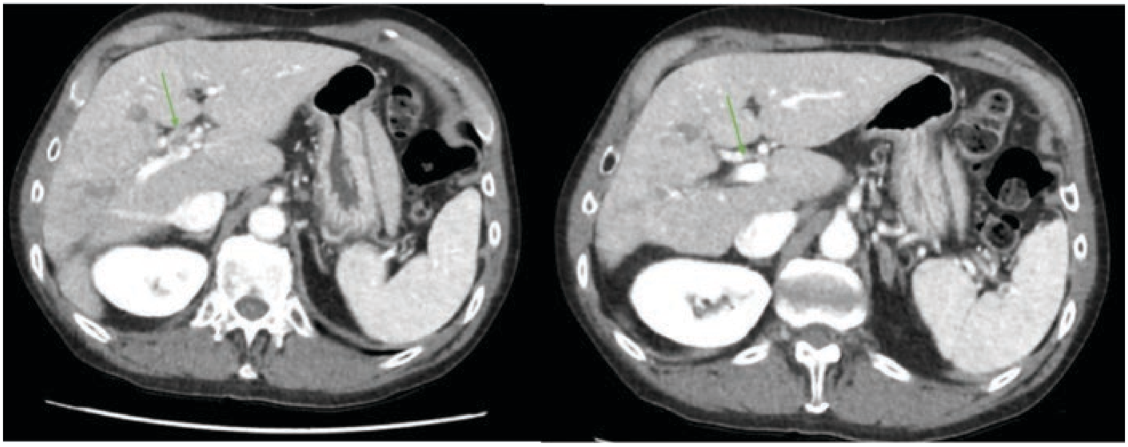

Figure 9 Filling defect in proximal portal vein (on the left) with expansion of vessel (on the right) consistent with extension into portal vein and associated tumor thrombus (courtesy of Radiology Department, St George Hospital Australia).

factor) has been approved for first-line therapy of advanced stage HCC following the phase III IM Brave trial (Bruix et al. 2021; Greten et al. 2021; Rimassa and Santoro 2009; Yau et al. 2022) (Table 6). This combination immunotherapy has shown significant improvement in progression-free survival compared with sorafenib monotherapy (19.2 versus 13.4 months, estimated HR for death 0.66, 95% CI 0.52–0.85). Largely based on these data, combination atezolizumab and bevacizumab is recommended in Child-Pugh A cirrhotics in non-resectable or advanced HCC who have not received prior systemic therapy, as in our case patient.

Tyrosine Kinase Inhibitors (Sorafenib, Lenvatinib)

First-line tyrosine kinase inhibitors (TKI) (lenvatinib and sorafenib) should be considered for patients that cannot have atezolizumab and bevacizumab combination therapy, due to contraindications (as outlined above). Sorafenib is a multi-targeted, orally active small molecule TKI that inhibits Raf kinase and the vascular endothelial growth factor receptor (VEGFR) intra-cellular kinase pathway. In fact, it was the first therapy to show an increase in median overall survival (Cheng et al. 2009; Yamashita et al. 2020).

Lenvatinib is an oral multi-kinase inhibitor that targets vascular growth factor receptor, fibroblast growth factors receptor, platelet-derived growth factors receptor, RET, and KIT. In a subsequent trial comparing lenvatinib with sorafenib, lenvatinib was found to be non-inferior to sorafenib, and progression-free survival was significantly higher in patients receiving lenvatinib compared to sorafenib (Yau et al. 2019). Thus, lenvatinib can use used an alternative first-line TKI to sorafenib.

Second-line Systemic Therapy

Second line treatment is used in patients who have had radiological or clinical disease progression on first-line treatment, and whose performance status and liver function are adequate to tolerate it. The choice of subsequent TKIs or immunotherapy is empiric, as there are no comparator trials in patients failing initial treatment.

Immunotherapy (Ipilimumab and Nivolumab, Pembroluzimab)

For patients who have progressed on first-line TKI (lenvatanib, sorafenib) with Child-Pugh A cirrhosis who have not undergone liver transplantation, combination therapy of nivolumab (programmed cell death 1 antibody) and ipilimumab (cytoxic T-lymphocyte associated 4 antibody), or pembroluzimab (programmed cell death 1 antibody) monotherapy is recommended. While second-line TKIs have been approved for this group, immune checkpoint inhibitors have a higher objective response rate and a more favorable side effect profile. These therapies have been approved by the FDA as second-line treatments for sorafenib-pretreated patients based off encouraging date from key phase II trials (Abou-Alfa et al. 2018; El-Khoueiry et al. 2017; Scheiner et al. 2019; Zhu et al. 2018).

Tyrosine Kinase Inhibitors (Regorafenib, Cabozantanib)

Regorafenib and cabozantanib are multi-kinase inhibitors with a similar mechanism of action to sorafenib, blocking the activity of multiple protein kinases involved in the angiogenesis and oncogenesis in the tumor microenvironment. In advanced HCC patients with preserved liver function who

Table 6 Landmark trials leading to FDA approvals for immunotherapy in advanced HCC (El-Khoury et al. 2017; Finn et al. 2020; Finn et al. 2020; Yau et al. 2022).

Therapy	Results	Comment
Nivolumab (dose-escalation vs dose-expansion) (Checkmate 040)	– Objective RR by investigator using RECIST criteria was 32%, 27% and 29% in arms A, B (dose-escalation) and C (dose-expansion) respectively. – Median overall survival was 22.8 months in arm A, 12.8 months in arm B, and 12.7 months in arm C. – Median duration of response was 17.5, 22.2 and 16.6 months in arms A, B and C respectively.	Arm A combination was thought to be a reasonable second line treatment option due to safety profile, durable response with significant overall response rates in patients previously treated with sorafenib in the first line setting.
Pembrolizumab vs placebo KEYNOTE-240	– Overall survival was 13.9 months in the pembrolizumab group compared with 10.6 months in the placebo group. – Objective response rate was 18.3% in pembrolizumab group compared with 4.4% in placebo group	Pembrolizumab showed improvement in overall survival and progression free survival over time in patients previously treated with sorafenib
Atezolizumab and bevacizumab vs sorafenib (IMBRAVE 150)	Primary endpoints 1. OS – At 6 months OS was 84.8% vs 72.2% – At 12 months OS was 67.2% vs 54.6% 2. PFS was 6.8 months (54.5%) vs 4.3 months (37.2%) Secondary endpoints 1. Objective RR was 27.3% vs 11.9% 2. Duration of response longer than 6 months was 87.6% vs 59.1%	This combination is now considered as first line treatment option for patients with advanced unresectable hepatocellular cancer if they have no contraindications.
Nivolumab vs sorafenib (Checkmate 459)	Primary endpoint 1. OS was 16.4 months vs 14.7 months. Additional endpoints 1. PFS was 3.7 months vs 3.8 months 2. Objective response rate was 57% vs 26%	Nivolumab did not increase the OS but was considered a safe alternative in patients who had contra-indications to TKIs and anti-angiogenic agents.

have progressed on sorafenib, both have shown to have a survival benefit (Brahmer et al. 2018; Kelley et al. 2017; Rimassa and Santoro 2009). Based on this data, regorafenib and cabozantinib have been approved as second-line treatments in patients who have progressed on sorafenib.

Side Effects of Systemic Treatment

Table 7 Side effects of systemic treatment (TKIs and immunotherapy).

Tyrosine kinase inhibitors	Immunotherapy
- Hypertension - Palmo-plantar erythrodysaesthesia - Skin rash - Cardiotoxicity - Anemia, thrombocytopenia - Nausea, vomiting - Electrolyte disturbances - Arthralgias - Pancreatic atrophy - Sarcopenia	- Skin toxicity - Colitis - Endocrinopathies, pneumonitis - Hepatotoxicity Specific to VEG-F inhibitors - Thromboembolic events - Bleeding - Poor wound healing - Hypertension - GI perforation - Proteinuria

How Do We Manage Immunotoxicity?

The toxicity profile of immunotherapy must be considered carefully on a case-by-case basis as it leads to a wide range of immune-mediated adverse effects due to impaired self-tolerance (Table 7). Most immunotherapy-related adverse effects (IRAE) are usually transient, but occasionally they can be severe and life-threatening (Schneider et al. 2021; Thompson et al. 2020). Overall, studies have reported less higher grade toxicity and therefore treatment discontinuation with monotherapy (less with PD-1/PDL-1 vs CTLA-4) compared to combination therapy (Pfister et al. 2021).

Multiple international guidelines like ASCO, ESMO, and NCCN generally recommend a similar management plan for treating IRAEs as mentioned below:

- Management varies according to organ system affected, in general, ICPi treatment can be continued with close monitoring for most grade 1 toxicities, except for some of the neurologic, hematologic, and cardiac toxicities.
- ICPi therapy should most likely be suspended for most grade 2 toxicities, with consideration of restarting treatment when symptoms have reverted to grade 1 or less. Corticosteroids may be considered for grade 2 toxicities. For

endocrinopathies immunotherapy should be withheld until adequate hormone replacement therapy has been initiated and treatment can be restarted after the acute symptoms have resolved. For patients with hypophysitis or adrenal insufficiency treatment can be restarted after adequate adrenal glucocorticoid replacement.

– Grade 3 toxicities generally warrant cessation of ICPis and the initiation of high-dose corticosteroids should not be delayed (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids can be slowly tapered over a period of at least 4 to 6 weeks and in some refractory cases where there is need for ongoing corticosteroid therapy, agents like infliximab, Mycophenolate or other immunosuppressive therapies can be considered.

– In general, permanent cessation of ICPis is recommended with all grade 4 toxicities, except for most of the endocrinopathies that can be managed with adequate hormone replacement.

Re-treatment after previous toxicity can be considered and is reasonably safe in most patients after having a risk benefit discussion and the decision to retreat also depends on multiple factors like severity of adverse effects, response to corticosteroid therapy, disease response to initial immunotherapy and availability of other alternative treatment options (Hui et al. 2013; Schneider et al. 2021).

Palliative Care

Case: A 74 year old male has a history of alcoholic Child-Pugh C cirrhosis, but did not comply with HCC surveillance. He had an incidental finding of multifocal HCC with IVC and portal vein invasion, after he presented with abdominal pain and weight loss. Given poor underlying liver function, he was not for surgery, locoregional treatment, or systemic treatment, so was commenced on best supportive treatment pathway in liaison with the palliative care team. He had worsening liver decompensation with progressive renal impairment, recurrent ascites and encephalopathy. He was transferred to a Palliative Care Unit for symptom management given his guarded prognosis, and passed away peacefully a week later.

Palliative care involves addressing and holistically managing the physical, emotional, and spiritual needs of patients and their families or carers as early in the treatment course as possible in order to improve patient quality of life (QoL) and to mitigate suffering (Baumann et al. 2015; Colagrande et al. 2016; Laube et al. 2021). This goal is best achieved in HCC through the PC multidisciplinary team, optimally consisting of specialist PC physicians and nurses, hepatologists, allied healthcare workers (including a social worker, physiotherapist, speech pathologist, occupational therapist, and dietitian), with access to chaplaincy and bereavement counsellors (Lubel et al. 2021).

What Are the Challenges of Palliative Care in HCC?

The nature of HCC necessitates the early introduction of PC. It is a complex disease underscored by an unpredictable course (Hope and Morrison 2011). This is largely attributable to the fact that it frequently occurs in the context of underlying end-stage liver disease (ESLD), with 85–90% of cases transpiring in this manner (Tarao et al. 2019). Accordingly, the health trajectory of patients presenting with both is unpredictable, characterized by episodic and acute exacerbations, as well as frequent hospitalizations and stabilizations (Befeler and Di Bisceglie 2002). Further, because of this underlying ESLD, HCC patients suffer from the symptoms of both liver failure and cancer (Graf and Stengel 2021). The former is characterized by the development of jaundice, ascites, variceal hemorrhage, and hepatic encephalopathy (Befeler and Di Bisceglie 2002), each with its own unique management challenges and prognostic implications. When combined with the classic constitutional clinical plethora of HCC, encompassing symptoms such as weight loss, anorexia, fever, and malaise (Lubel et al. 2021), coupled with the long and protracted treatment journey (Lubel et al. 2021), patients with this typical dual presentation are subject to severe physical and psychological burden (Bakitas et al. 2009).

What Does Palliative Care in HCC Involve?

Importantly, palliative should be delivered congruently with disease-modifying therapy early in the management of HCC (Temel et al. 2010). Several randomized controlled trials (RCTs) studying advanced cancers have supported this (Vanbutsele et al. 2020; Woodrell et al. 2018; Zimmermann et al. 2014).

The services provided by PC fall under four main headings, including symptom management, care coordination, psychosocial support, and decisional support. Their implementation should extend across all stages of HCC including the early stages, when curative treatments are still available (Table 8) (Lubel et al. 2021).

Importantly, these four domains have a significant role in mitigating the strenuous patient experience for those with HCC (Tarao et al. 2019, 182). Symptom management should include pharmacological control of pain, and choice of analgesia should take into consideration degree of hepatic function, and co-existent complications such as hepatic encephalopathy or hepatorenal syndrome. Given the unpredictable course of HCC, advanced care planning should be instituted early. Psychosocial support is important given the severe psychological burden of HCC, and clinicians should work to identify religious and spiritual needs of the patient and their families, and refer to support groups when appropriate.

Table 8 Potential role of palliative care across all stages of HCC (Adapted from Lubel et al. 2021).

HCC stage	HCC therapy options	Typical symptoms	*Role of palliative care in each stage*
Early (BCLC Stage 0-A) Single nodule <2 cm, PST 0, Child-Pugh A	- Liver resection - Liver transplant - Ablation (RF/PEI)	- Adverse effects of treatment including pain, infection, fever	- Symptom control - Disease education - Advanced care planning and goals of care discussion
Intermediate (BCLC Stage B) Multinodular, PS 0, Child-Pugh A/B	- TACE	- Adverse effects of treatment including nausea, vomiting, pain, fever, fatigue - Local symptoms of primary tumor - Extrahepatic symptoms	- Address the physical, psychosocial, and spiritual needs of patients through symptom control, counseling and chaplain services respectively - Assistance with decision-making and navigation through treatment pathways
Advanced (BCLC Stage C) Portal invasion, N1, M1, PS 1–2, Child-Pugh B	- Systemic chemotherapy (e.g. Sorafenib)	- Adverse effects of treatment (skin reaction, diarrhea, anorexia, fatigue) - Local symptoms of primary tumor - Extrahepatic symptoms	
Late-stage/terminal (BCLC Stage D) PST >2, Child-Pugh C	- Best supportive care (appropriate palliative care)	- Local symptoms of primary tumor - Extrahepatic symptoms (fatigue, anorexia) - Liver failure (jaundice, ascites, and encephalopathy) - Metastatic disease (symptoms related to system of metastases, e.g. dyspnea, pain)	- Symptom control - End-of-life care - Provision of resources (e.g. hospice unit and community equipment) -Family support and bereavement counseling

Key Take Home Messages

- HCC surveillance (with liver US +/– AFP every 6 months) recommended to be undertaken in all cirrhotics, as well as in non-cirrhotics with chronic HBV infection who are at increased risk of HCC.
- It is recommended that the BCLC staging should be used as the framework for HCC management; and the management choice should take into account the individual's liver function, functional status as well as psychosocial circumstances.
- The management of HCC ideally should be determined by a multidisciplinary team to optimize patient care.
- Liver resection is a first-line therapy option in suitable patients with HCC where there is preserved liver function, sufficient liver remnant, and absence of significant portal hypertension.
- Liver transplantation should be considered for patients with HCC within transplant criteria who are not suitable for curative hepatic resection or ablative therapy.
- Patients with HCC initially beyond transplant criteria may be considered for liver transplantation after successful downstaging to within standard transplant criteria.
- Ablative therapy and SIRTEX are recommended as a curative locoregional therapy in suitable patients with very early or early (BCLC Stage 0 or A) HCC, or in patients who are not candidates for surgery or liver transplantation.
- SIRT or SBRT may be considered in select patients with intermediate or locally advanced HCC for local tumor control.
- Patients with advanced HCC (BCLC Stage C) or multifocal HCC that is not amenable to curative or locoregional therapy (BCLC Stage B) should be offered systemic therapy, with immunotherapy or multi-kinase inhibitors (sorafenib or lenvatinib) as first-line therapy options depending on patient's comorbidities.
- Patients with incurable HCC should be introduced to supportive care services early in their management.
- Hepatocellular carcinoma (HCC) continues to be an increasing indication for liver transplantation (LTx) in patients with liver cirrhosis.
- Milan criteria remain a reference in the liver transplant assessment of patients with HCC.
- There is an increasing role of downstaging procedures permitting transplantation in tumors exceeding Milan criteria however no randomized data exists to support any particular modality used in downstaging

What's not known

- Liver allocation to patients with HCC remains a great challenge with scoring systems being systematically updated and refined in order to ensure a fair distribution of organs.
- Prevention of HCC recurrence after LTx continues to be a challenge and the potential preventive role of immunosuppression with mTOR inhibitors need to be established.

Areas for Further Research

- Further investigation is required in predicting risk of HCC recurrence following resection, liver transplantation, and locoregional therapies.
- Neoadjuvant or adjuvant therapies for high risk patients (for example, with lymphovascular invasion) are still under investigation.
- The role of radiotherapy in the neoadjuvant setting prior to surgical resection or liver transplantation has not yet been outlined.
- Transarterial embolization in combination with systemic therapy is currently under investigation.
- There are no clinical or molecular biomarkers established as of yet to predict response to first or second-line systemic treatments. Molecular characterization of the HCC tumor microenvironment are currently under investigation, that may enable the development of biomarkers that can be used in routine clinical practice to predict prognosis and treatment response; as exists in breast and lung malignancy for example.

Trusted Websites for Further Reading

1 EASL Clinical Practice Guidelines: Liver Transplantation: https://easl.eu/wp-content/uploads/2018/10/Liver-Transplantation-English-report.pdf

2 Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases: https://www.aasld.org/sites/default/files/2022-06/AASLD_2018_HCC_Guidance_on_Diagnosis%2C_Staging_and_Management_hep_29913.pdf

3 Milan criteria for liver transplantation: https://www.mdcalc.com/calc/3900/milan-criteria-liver-transplantation

4 Scoring system for liver transplantation in Hepatocellular Carcinoma (METROTICKET PROJECT): http://www.hcc-olt-metroticket.org

References

Abou-Alfa, G.K., Meyer, T., Cheng, A.L. et al. (2018). Cabozantinib (C) vs. placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: results from the randomized phase III CELESTIAL trial. *J Clin Oncol* 36.

Abulkhir, A., Limongelli, P., Healey, A.J. et al. (2008). Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 247 (1): 49–57.

Adam, R., Azoulay, D., Castaing, D. et al. (2003). Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? *Ann Surg* 238 (4): 508–518. discussion 18–9.

Alonzo, M., Bos, A., Bennett, S., and Ferral, H. (2015). The EmprintTM ablation system with thermosphereTM technology: one of the Newer next-Generation microwave ablation technologies. *Semin Interv Radiol* 32 (4): 335–338.

Aoki, T. and Kubota, K. (2016). Preoperative portal vein embolization for hepatocellular carcinoma: consensus and controversy. *World J Hepatol* 8 (9): 439–445.

Apisarnthanarax, S., Barry, A., Cao, M. et al. (2022). External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. *Pract radiat oncol* 12 (1): 28–51.

Au, J.S. and Frenette, C.T. (2015). Management of hepatocellular carcinoma: current status and future directions. *Gut and Liver* 9 (4): 437–448.

Bakitas, M., Lyons, K.D., Hegel, M.T. et al. (2009). Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the project ENABLE II randomized controlled trial. *JAMA* 02 (7): 741–749.

Baumann, A.J., Wheeler, D.S., James, M. et al. (2015). Benefit of early palliative care intervention in end-stage liver disease patients awaiting liver transplantation. *J Pain Symptom Manag* 50 (6): 882–6.e2.

European Association for the Study of the Liver. (2018). EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 69 (1): 182–236.

Befeler, A.S. and Di Bisceglie, A.M. (2002). Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology* 122: 1609–1619.

Benson, A.I.B., D'Angelica, M.I., Abbott, D.E. et al. (2021). Hepatobiliary cancers, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw: JNCCN* 19 (5): 541–565.

Berzigotti, A., Reig, M., Abraldes, J.G. et al. (2015). Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. *Hepatology* 61 (2): 526–536.

Bolondi, L., Cillo, U., Colombo, M. et al. (2013). Position paper of the Italian association for the study of the liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma. *Dig Liver Dis* 45 (9): 712–723.

Brahmer, J.R., Lacchetti, C., and Thompson, J.A. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline summary. *J Oncol Pract* 14: 247–249.

Brown, K.T., Do, R.K., Gonen, M. et al. (2016). Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol: Off J Am Soc Clin Oncol* 34 (17): 2046–2053.

Bruix, J., Chan, S.L., Galle, P.R. et al. (2021). Systemic treatment of hepatocellular carcinoma: an EASL position paper. *J Hepatol* 75 (4): 960–974.

Cescon, M., Colecchia, A., Cucchetti, A. et al. (2012). Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. *Ann Surg* 256 (5): 706–712. discussion 12–3.

Cescon, M., Cucchetti, A., Ravaioli, M., and Pinna, A.D. (2013). Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol* 58 (3): 609–618.

Cheng, A.L., Kang, Y.K., Chen, Z. et al. (2009). Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 10 (1): 25–34.

Chew, V., Lee, Y.H., Pan, L. et al. (2019). Immune activation underlies a sustained clinical response to Yttrium-90 radioembolisation in hepatocellular carcinoma. *Gut* 68 (2): 335–346.

Chirica, M., Scatton, O., Massault, P.P. et al. (2008). Treatment of stage IVA hepatocellular carcinoma: should we reappraise the role of surgery? *Arch Surg* 143 (6): 538–543. discussion 43.

Cho, E., Cho, H.A., Jun, C.H. et al. (2019). A review of hepatocellular carcinoma in elderly patients focused on management and outcomes. *In Vivo* 33 (5): 1411–1420.

Cho, Y.K., Kim, J.K., Kim, W.T., and Chung, J.W. (2010). Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. *Hepatology* 51 (4): 1284–1290.

Chuang, Y.H., Ou, H.Y., Lazo, M.Z. et al. (2018). Predicting post-hepatectomy liver failure by combined volumetric, functional MR image and laboratory analysis. *Liver Int* 38 (5): 868–874.

Ciria, R., Cherqui, D., Geller, D.A. et al. (2016). Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. *Ann Surg* 263 (4): 761–777.

Citterio, D., Facciorusso, A., Sposito, C. et al. (2016). Hierarchic interaction of factors associated with liver decompensation after resection for hepatocellular carcinoma. *JAMA Surg* 151 (9): 846–853.

Clavien, P.A., Lesurtel, M., Bossuyt, P.M. et al. (2012). Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 13 (1): e11–22.

Colagrande, S., Inghilesi, A.L., Aburas, S. et al. (2016). Challenges of advanced hepatocellular carcinoma. *World J Gastroenterol* 22 (34): 7645–7659.

Cucchetti, A., Piscaglia, F., Cescon, M. et al. (2013). Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *J Hepatol* 59 (2): 300–307.

Dawson, L.A. (2011). Overview: where does radiation therapy fit in the spectrum of liver cancer local-regional therapies? *Sem Rad Oncol* 21 (4): 241–246. WB Saunders.

De Gasperi, A., Mazza, E., and Prosperi, M. (2016). Indocyanine green kinetics to assess liver function: ready for a clinical dynamic assessment in major liver surgery? *World J Hepatol* 8 (7): 355–367.

Dello, S.A., Lodewick, T.M., van Dam, R.M. et al. (2013). Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. *HPB (Oxford)* 15 (3): 165–169.

Doyle, A., Gorgen, A., Muaddi, H. et al. (2019). Outcomes of radiofrequency ablation as first-line therapy for hepatocellular carcinoma less than 3 cm in potentially transplantable patients. *J Hepatol* 70 (5): 866–873.

El-Khoueiry, A.B., Sangro, B., Yau, T. et al. (2017). Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 6736: 1–11.

El-Serag, H.B. and Rudolph, K.L. (2007). Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 132 (7): 2557–2576.

Esposito, F., Lim, C., Lahat, E. et al. (2019). Combined hepatic and portal vein embolization as preparation for major hepatectomy: a systematic review. *HPB (Oxford)* 21 (9): 1099–1106.

Ettorre, G.M., Sandri, G.B.L., Laurenzi, A. et al. (2017). Yttrium-90 radioembolization for hepatocellular carcinoma prior to liver transplantation. *World J Surg* 41 (1): 241–249.

Facciorusso, A., Di Maso, M., and Muscatiello, N. (2016). Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Hyperthermia: Off J Eur Soc Hyperthermic Oncol, North Am Hyperthermia Group* 32 (3): 339–344.

Fan, S.T., Lo, C.M., Lai, E.C. et al. (1994). Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med* 331 (23): 1547–1552.

Farges, O., Belghiti, J., Kianmanesh, R. et al. (2003). Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 237 (2): 208–217.

Farges, O., Malassagne, B., Flejou, J.F. et al. (1999). Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg* 229 (2): 210–215.

Finn, R.S., Qin, S., Ikeda, M. et al. (2020). Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. *New Engl J Med* 382 (20): 1894–1905.

Finn, R.S., Ryoo, B.Y., Merle, P. et al. (2020). Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol: Off J Am Soc Clin Oncol* 38 (3): 193–202.

Forner, A., Gilabert, M., Bruix, J., and Raoul, J.-L. (2015). Heterogeneity of intermediate-stage HCC necessitates personalized management including surgery. *Nat Rev Clin Oncol* 12 (1): 10-.

Fukami, Y., Kaneoka, Y., Maeda, A. et al. (2020). Liver resection for multiple hepatocellular carcinomas: a Japanese Nationwide survey. *Ann Surg* 272 (1): 145–154.

Fuks, D., Dokmak, S., Paradis, V. et al. (2012). Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. *Hepatology* 55 (1): 132–140.

Glantzounis, G.K., Paliouras, A., Stylianidi, M.C. et al. (2018). The role of liver resection in the management of intermediate and advanced stage hepatocellular carcinoma. A systematic review. *Eur J Surg Oncol* 44 (2): 195–208.

Goldberg, S.N., Hahn, P.F., Tanabe, K.K. et al. (1998). Percutaneous radiofrequency tissue ablation: does Perfusion-mediated tissue cooling limit coagulation Necrosis? *J Vasc Interv Radiol: JVIR* 9 (1 Pt 1): 101–111.

Gordan, J.D., Kennedy, E.B., Abou-Alfa, G.K. et al. (2020). Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. *J Clin Oncol: Off J Am Soc Clin Oncol* 38 (36): 4317–4345.

Graf, J. and Stengel, A. (2021). Psychological burden and psycho-oncological interventions for patients with hepatobiliary cancers–A systematic review. *Front Psychol.* 12:662777.

Greten, T.F., Abou-Alfa, G.K., Cheng, A.L. et al. (2021 September). Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma. *J Immunother Cancer* 9 (9): e002794.

Halazun, K.J., Hardy, M.A., Rana, A.A. et al. (2009). Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg* 250 (1): 141–151.

Halazun, K.J., Tabrizian, P., Najjar, M. et al. (2018). Is it time to abandon the Milan criteria?: results of a Bicoastal US collaboration to redefine hepatocellular carcinoma liver transplantation selection policies. *Ann Surg* 268 (4): 690–699.

Heimbach, J.K., Kulik, L.M., Finn, R.S. et al. (2018). AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology (Baltimore, Md)* 67 (1): 358–380.

Hoekstra, L.T., van Lienden, K.P., Doets, A. et al. (2012). Tumor progression after preoperative portal vein embolization. *Ann Surg* 256 (5): 812–817. discussion 7–8.

Hope, A.A. and Morrison, R.S. (2011). Integrating palliative care with chronic liver disease care. *J Palliat Care* 27 (1): 20–27.

Huang, S.Y. and Aloia, T.A. (2017). Portal Vein Embolization: state-of-the-art technique and options to improve liver hypertrophy. *Visc Med* 33 (6): 419–425.

Huang, T.H., Hsieh, C.C., Kuo, L.M. et al. (2019). Malnutrition associated with an increased risk of postoperative complications following hepatectomy in patients with hepatocellular carcinoma. *HPB (Oxford)* 21 (9): 1150–1155.

Hui, D., De La Cruz, M., Mori, M. et al. (2013). Concepts and definitions for "supportive care," "best supportive care," "palliative care," and "hospice care" in the published literature, dictionaries, and textbooks. *Support Care Cancer: Off J Multinational Ass Support Care Cancer* 21 (3): 659–685.

Hwang, J.P., Feld, J.J., Hammond, S.P. et al. (2020). Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. *J Clin Oncol* 38 (31): 3698–3715.

Ilhan, H., Goritschan, A., Paprottka, P. et al. (2015). Systematic evaluation of tumoral 99mTc-MAA uptake using SPECT and SPECT/CT in 502 patients before 90Y Radioembolization. *J Nucl Med: Off Publication, Soc Nucl Med* 56 (3): 333–338.

Imamura, H., Seyama, Y., Kokudo, N. et al. (2003). One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 138 (11): 1198–1206. discussion 206.

Ioannou, G.N., Splan, M.F., Weiss, N.S. et al. (2007). Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 5 (8): 938–945, 45.

Ishizawa, T., Hasegawa, K., Aoki, T. et al. (2008). Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 134 (7): 1908–1916.

Itoh, S., Yoshizumi, T., Shirabe, K. et al. (2017). Functional remnant liver assessment predicts liver-related morbidity after hepatic resection in patients with hepatocellular carcinoma. *Hepatol Res* 47 (5): 398–404.

Iwatsuki, S., Gordon, R.D., Shaw, B.W., Jr., and Starzl, T.E. (1985). Role of liver transplantation in cancer therapy. *Ann Surg* 202 (4): 401–407.

Izumi, N., Hasegawa, K., Nishioka, Y. et al. (2019). A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small hepatocellular carcinoma (SURF trial). *J Clin Oncol* 37 (15_suppl): 4002-.

Izzo, F., Granata, V., Grassi, R. et al. (2019). Radiofrequency ablation and microwave ablation in liver tumors: an update. *Oncologist* 24 (10): e990–1005.

Jang, J.W., You, C.R., Kim, C.W. et al. (2010). Benefit of downsizing hepatocellular carcinoma in a liver transplant population. *Aliment Pharmacol Ther* 31 (3): 415–423.

Kelley, R.K., Verslype, C., Cohn, A.L. et al. (2017). Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study. *Ann Oncol* 28: 528–534.

Kim, G.A., Shim, J.H., Yoon, S.M. et al. (2015). Comparison of chemoembolization with and without radiation therapy and sorafenib for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. *J Vasc Interv Radiol* 26 (3): 320–329 e326.

Kim, J.W., Shin, S.S., Kim, J.K. et al. (2013). Radiofrequency ablation combined with transcatheter arterial chemoembolization for the treatment of single hepatocellular carcinoma of 2 to 5 Cm in diameter: comparison with surgical resection. *Korean J Radiol: Off J Korean Radiol Soc* 14 (4): 626–635.

Kim, T.H., Koh, Y.H., Kim, B.H. et al. (2021 March 1). Proton beam radiotherapy vs. Radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase III trial. *J Hepatol* 74 (3): 603–612.

Kishida, N., Hibi, T., Itano, O. et al. (2015). Validation of hepatectomy for elderly patients with hepatocellular carcinoma. *Ann Surg Oncol* 22 (9): 3094–3101.

Kokudo, T., Hasegawa, K., Matsuyama, Y. et al. (2016). Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. *J Hepatol* 65 (5): 938–943.

Kokudo, T., Hasegawa, K., Matsuyama, Y. et al. (2017). Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: a Japanese nationwide survey. *Hepatology* 66 (2): 510–517.

Kuroda, S., Tashiro, H., Kobayashi, T. et al. (2011). Selection criteria for hepatectomy in patients with hepatocellular carcinoma classified as Child-Pugh class B. *World J Surg* 35 (4): 834–841.

Lammer, J., Malagari, K., Vogl, T. et al. (2010). Prospective randomized study of Doxorubicin-Eluting-Bead Embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovascul Interv Radiol* 33 (1): 41–52.

Laube, R., Sabih, A.H., Strasser, S.I. et al. (2021). Palliative care in hepatocellular carcinoma. *J gastroenterol hepatol* 36 (3): 618–628.

Lee, H.J., Kim, J.W., Hur, Y.H. et al. (2019). Conventional chemoembolization plus radiofrequency ablation versus surgical resection for single, medium-sized hepatocellular carcinoma: propensity-score matching analysis. *J Vasc Interv Radiol: JVIR* 30 (3): 284–92.e1.

Lee, K.W., Suh, S.W., Choi, Y. et al. (2017). Macrovascular invasion is not an absolute contraindication for living donor liver transplantation. *Liver Transpl* 23 (1): 19–27.

Lencioni, R., Kudo, M., Ye, S.-L. et al. (2014). GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment with sorafeNib): second interim analysis. *Int J Clin Pract* 68 (5): 609–617.

Lencioni, R., Thierry de Baere, M.C.S., Rilling, W.S., and Geschwind, J.H. (2016). Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. *Hepatology* 64 (1): 106–116.

Lewandowski, R.J., Kulik, L.M., Riaz, A. et al. (2009). A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus Radioembolization. *Am J Transplant: Off J Am Soc Transplant Am Soc Transplant Surg* 9 (8): 1920–1928.

Liu, Z., Jiang, Y., Yuan, H. et al. (2019). The trends in incidence of primary liver cancer caused by specific etiologies: results from the global burden of disease study 2016 and implications for liver cancer prevention. *J Hepatol* 70: 674–683.

Llop, E., Berzigotti, A., Reig, M. et al. (2012). Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. *J Hepatol* 56 (1): 103–108.

Llovet, J.M., Bru, C., and Bruix, J. (1999a). Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 19: 329–338.

Llovet, J.M. and Bruix, J. (2003). Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 37 (2): 429–442.

Llovet, J.M., Bustamante, J., Castells, A. et al. (1999b). Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 29: 62–67.

Llovet, J.M., Real, M.I., Montaña, X. et al. (2002). Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 359 (9319): 1734–1739.

Lubel, J.S., Roberts, S.K., Strasser, S.I. et al. (2021). Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. *Med J Aust* 214 (10): 475–483.

Majno, P., Lencioni, R., Mornex, F. et al. (2011). Is the treatment of hepatocellular carcinoma on the waiting list necessary? *Liver Transpl* 17 (Suppl 2): S98–108.

Makuuchi, M., Kosuge, T., Takayama, T. et al. (1993). Surgery for small liver cancers. *Semin Surg Oncol* 9 (4): 298–304.

Maluccio, M.A., Covey, A.M., Porat, L.B. et al. (2008). Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol: JVIR* 19 (6): 862–869.

Mazzaferro, V., Citterio, D., Bhoori, S. et al. (2020). Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol* 21 (7): 947–956.

Mazzaferro, V., Llovet, J.M., Miceli, R. et al. (2009). Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 10 (1): 35–43.

Mazzaferro, V., Regalia, E., Doci, R. et al. (1996). Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334 (11): 693–699.

Mehta, N., Heimbach, J., Harnois, D.M. et al. (2017). Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. *JAMA Oncol* 3 (4): 493–500.

Molina, V., Sampson-Dávila, J., Ferrer, J. et al. (2018). Benefits of laparoscopic liver resection in patients with hepatocellular carcinoma and portal hypertension: a case-matched study. *Surg Endosc* 32 (5): 2345–2354.

Morise, Z., Ciria, R., Cherqui, D. et al. (2015). Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. *J Hepatobiliary Pancreat Sci* 22 (5): 342–352.

N'Kontchou, G., Mahamoudi, A., Aout, M. et al. (2009). Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology* 50 (5): 1475–1483.

Ni, J.Y., Liu, S.S., Xu, L.F. et al. (2013). Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol: WJG* 19 (24): 3872–3882.

Nishikawa, H., Arimoto, A., Wakasa, T. et al. (2013). Surgical resection for hepatocellular carcinoma: clinical outcomes and safety in elderly patients. *Eur J Gastroenterol Hepatol* 25 (8): 912–919.

Nishio, T., Taura, K., Koyama, Y. et al. (2016). Prediction of posthepatectomy liver failure based on liver stiffness measurement in patients with hepatocellular carcinoma. *Surgery* 159 (2): 399–408.

Okabayashi, T., Shima, Y., Morita, S. et al. (2017). Liver function assessment using technetium 99m-Galactosyl Single-photon emission computed tomography/CT fusion imaging: a prospective trial. *J Am Coll Surg* 225 (6): 789–797.

Okamura, Y., Sugiura, T., Ito, T. et al. (2018). The short- and long-term outcomes in elderly patients with hepatocellular carcinoma after curative surgery: a case-controlled study with propensity score matching. *Eur Surg Res* 59 (5–6): 380–390.

Oldhafer, K.J., Stavrou, G.A., and van Gulik, T.M. (2016). ALPPS–Where do we stand, where do we go?: eight recommendations from the first international expert meeting. *Ann Surg* 263 (5): 839–841.

Olthof, P.B., Tomassini, F., Huespe, P.E. et al. (2017). Hepatobiliary scintigraphy to evaluate liver function in associating liver partition and portal vein ligation for staged hepatectomy: liver volume overestimates liver function. *Surgery* 162 (4): 775–783.

Otsuji, H., Yokoyama, Y., Ebata, T. et al. (2015). Preoperative sarcopenia negatively impacts postoperative outcomes following major hepatectomy with extrahepatic bile duct resection. *World J Surg* 39 (6): 1494–1500.

Pawlik, T.M., Poon, R.T., Abdalla, E.K. et al. (2005). Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. *Surgery* 137 (4): 403–410.

Peng, Z.W., Wei, M., Chen, S. et al. (2018). Combined transcatheter arterial chemoembolization and radiofrequency ablation versus hepatectomy for recurrent hepatocellular carcinoma after initial surgery: a propensity score matching study. *Eur Radiol* 28 (8): 3522–3531.

Perisetti, A., Goyal, H., Yendala, R. et al. (2022). Sarcopenia in hepatocellular carcinoma: current knowledge and future directions. *World J Gastroenterol* 28 (4): 432–448.

Pesi, B., Ferrero, A., Grazi, G.L. et al. (2015). Liver resection with thrombectomy as a treatment of hepatocellular carcinoma with major vascular invasion: results from a retrospective multicentric study. *Am J Surg* 210 (1): 35–44.

Pfister, D., Núñez, N.G., Pinyol, R. et al. (2021). NASH limits anti-tumour surveillance in immunotherapy-treated HCC. *Nature* 592 (7854): 450–456.

Pinter, M., Scheiner, B., and Peck-Radosavljevic, M. (2021). Immunotherapy for advanced hepatocellular carcinoma: a focus on special subgroups. *Gut* 70 (1): 204–214.

Piscaglia, F. and Ogasawara, S. (2018). Patient selection for transarterial chemoembolization in hepatocellular Carcinoma: importance of benefit/Risk assessment. *Liver Cancer* 7 (1): 104–119.

Pompili, M., Saviano, A., de Matthaeis, N. et al. (2013). Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. *J Hepatol* 59 (1): 89–97.

Ravaioli, M., Grazi, G.L., Piscaglia, F. et al. (2008). Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 8 (12): 2547–2557.

Reig, M., Forner, A., Rimola, J. et al. (2022). BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 76 (3): 681–693.

Rimassa, L. and Santoro, A. (2009). Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. *Expert Rev Anticancer Ther* 9 (6): 739–745.

Roayaie, S., Jibara, G., Taouli, B., and Schwartz, M. (2013). Resection of hepatocellular carcinoma with macroscopic vascular invasion. *Ann Surg Oncol* 20 (12): 3754–3760.

Ruzzenente, A., Valdegamberi, A., Campagnaro, T. et al. (2011). Hepatocellular carcinoma in cirrhotic patients with portal hypertension: is liver resection always contraindicated? *World J Gastroenterol* 17 (46): 5083–5088.

Salem, R., Gordon, A.C., Mouli, S. et al. (2016). Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 151 (6): 1155–63.e2.

Salem, R., Johnson, G.E., Kim, E. et al. (2021). Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. *Hepatology* 74 (5): 2342–2352.

Sangro, B., Sarobe, P., Hervás-Stubbs, S., and Melero, I. (2021). Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 18 (8): 525–543.

Santambrogio, R., Barabino, M., Scifo, G. et al. (2017). Effect of age (over 75 Years) on postoperative complications and survival in patients undergoing hepatic resection for hepatocellular carcinoma. *J Gastrointest Surg* 21 (4): 657–665.

Santambrogio, R., Kluger, M.D., Costa, M. et al. (2013). Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? *Witowski* 15 (1): 78–84.

Santopaolo, F., Lenci, I., Milana, M. et al. (2019). Liver transplantation for hepatocellular carcinoma: where do we stand? *World J Gastroenterol* 25 (21): 2591–2602.

Sapisochin, G., Goldaracena, N., Laurence, J.M. et al. (2016). The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. *Hepatology (Baltimore, Md)* 64 (6): 2077–2088.

Scheiner, B., Kirstein, M.M., Hucke, F. et al. (2019). Programmed cell death protein-1 (PD-1)- targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. *Aliment Pharmacol Ther* 49: 1323–1333.

Schneider, B.J., Naidoo, J., Santomasso, B.D. et al. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol* 39: 4073–4126.

Schnitzbauer, A.A. (2017). A comparison of pitfalls after ALPPS stage 1 or portal Vein Embolization in small-for-size setting Hepatectomies. *Visc Med* 33 (6): 435–441.

Shanker, M.D., Liu, H.Y., Lee, Y.Y. et al. (2021). Stereotactic radiotherapy for hepatocellular carcinoma: expanding the multidisciplinary armamentarium. *J Gastroenterol Hepatol* 36 (4): 873–884.

Shanker, M.D., Moodaley, P., Soon, W. et al. (2021 December). Stereotactic ablative radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of local control, survival and toxicity outcomes. *J Med Imag Radiat Oncol* 65 (7): 956–968.

Shiina, S., Tateishi, R., Arano, T. et al. (2012). Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol* 107 (4): 569–577. quiz 78.

Shindoh, J., Tzeng, C.W.D., and Vauthey, J.N. (2012). Portal vein embolization for hepatocellular carcinoma. *Liver Cancer* 1 (3–4): 159–167.

Sieghart, W., Hucke, F., and Peck-Radosavljevic, M. (2015). Transarterial Chemoembolization: modalities, indication, and patient selection. *J Hepatol* 62 (5): 1187–1195.

Simpson, A.L., Geller, D.A., Hemming, A.W. et al. (2014). Liver planning software accurately predicts postoperative liver volume and measures early regeneration. *J Am Coll Surg* 219 (2): 199–207.

Sposito, C., Battiston, C., Facciorusso, A. et al. (2016). Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. *Br J Surg* 103 (7): 871–880.

Strasberg, S.M. (2005). Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 12 (5): 351–355.

Sung, H., Ferlay, J., Siegel, R.L. et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin* 71: 209–249.

Tarao, K., Nozaki, A., Ikeda, T. et al. (2019). Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases-meta-analytic assessment. *Cancer Med* 8 (3): 1054–1065.

Temel, J.S., Greer, J.A., Muzikansky, A. et al. (2010). Early palliative care for patients with metastatic non-small-cell lung cancer. *New Engl J Med* 363 (8): 733–742.

Thompson, J.A., Schneider, B.J., Brahmer, J. et al. (2020). NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. *J Natl Compr Canc Netw* 18: 230–241.

Torzilli, G., Belghiti, J., Kokudo, N. et al. (2013). A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg* 257 (5): 929–937.

Toso, C., Meeberg, G., Hernandez-Alejandro, R. et al. (2015). Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: a prospective validation. *Hepatology (Baltimore, Md)* 62 (1): 158–165.

Troisi, R.I., Berardi, G., Morise, Z. et al. (2021). Laparoscopic and open liver resection for hepatocellular carcinoma with Child-Pugh B cirrhosis: multicentre propensity score-matched study. *Br J Surg* 108 (2): 196–204.

Vanbutsele, G., Van Belle, S., Surmont, V. et al. (2020). The effect of early and systematic integration of palliative care in oncology on quality of life and health care use near the end of life: a randomised controlled trial. *Eur J Cancer (Oxford, England: 1990)* 124: 186–193.

Vasnani, R., Ginsburg, M., Ahmed, O. et al. (2016). Radiofrequency and microwave ablation in combination with transarterial Chemoembolization induce equivalent histopathologic coagulation necrosis in hepatocellular carcinoma patients bridged to liver transplantation. *Hepatobiliary Surg Nutr* 5 (3): 225–233.

Vauthey, J.N., Chaoui, A., Do, K.A. et al. (2000). Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 127 (5): 512–519.

Vietti Violi, N., Duran, R., Guiu, B. et al. (2018). Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 3 (5): 317–325.

Vivarelli, M., Cucchetti, A., Piscaglia, F. et al. (2005). Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. *Liver Transpl* 11 (5): 497–503.

Vouche, M., Lewandowski, R.J., Atassi, R. et al. (2013). Radiation Lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J Hepatol* 59 (5): 1029–1036.

Wei, A.C., Tung-Ping Poon, R., Fan, S.T., and Wong, J. (2003). Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *Br J Surg* 90 (1): 33–41.

Witowski, J., Rubinkiewicz, M., Mizera, M. et al. (2019). Meta-analysis of short- and long-term outcomes after pure laparoscopic versus open liver surgery in hepatocellular carcinoma patients. *Surg Endosc* 33 (5): 1491–1507.

Wong, J.S., Wong, G.L., Chan, A.W. et al. (2013). Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. *Ann Surg* 257 (5): 922–928.

Woodrell, C.D., Hansen, L., Schiano, T.D., and Goldstein, N.E. (2018). Palliative care for people with hepatocellular carcinoma, and specific benefits for older adults. *Clin Thera* 40: 512–525.

Wu, F.H., Shen, C.H., Luo, S.C. et al. (2019). Liver resection for hepatocellular carcinoma in oldest old patients. *World J Surg Oncol* 17 (1): 1.

Wu, H., Xing, H., Liang, L. et al. (2019). Real-world role of performance status in surgical resection for hepatocellular carcinoma: a multicenter study. *Eur J Surg Oncol* 45 (12): 2360–2368.

Yamada, S., Shimada, M., Miyake, H. et al. (2012). Outcome of hepatectomy in super-elderly patients with hepatocellular carcinoma. *Hepatol Res* 42 (5): 454–458.

Yamanaka, J., Saito, S., and Fujimoto, J. (2007). Impact of preoperative planning using virtual segmental volumetry on liver resection for hepatocellular carcinoma. *World J Surg* 31: 1249–1255.

Yamashita, T., Kudo, M., Ikeda, K. et al. (2020). REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset. *J Gastroenterol* 55 (1): 113–122.

Yao, F.Y., Bass, N.M., Nikolai, B. et al. (2003). A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. *Liver Transpl* 9 (7): 684–692.

Yao, F.Y., Ferrell, L., Bass, N.M. et al. (2001). Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology (Baltimore, Md)* 33 (6): 1394–1403.

Yao, F.Y., Xiao, L., Bass, N.M. et al. (2007). Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 7: 2587–2596.

Yau, T., Kang, Y.-K., Kim, T.-Y. et al. (2019). Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (PTS) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. *J Clin Oncol* 37: 4012.

Yau, T., Park, J.W., Finn, R.S. et al. (2022). Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 23 (1): 77–90.

Yoon, S.M., Ryoo, B.Y., Lee, S.J. et al. (2018). Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized clinical trial. *JAMA oncol* 4 (5): 661–669.

You, D.D., Kim, D.G., Seo, C.H. et al. (2017). Prognostic factors after curative resection hepatocellular carcinoma and the surgeon's role. *Ann Surg Treat Res* 93 (5): 252–259.

Young, S. and Golzarian, J. (2020). Locoregional therapies in the treatment of 3- to 5-Cm hepatocellular carcinoma: critical review of the literature. *AJR Am J Roentgenol* 215 (1): 223–234.

Yu, J., Yu, X., Han, Z. et al. (2017). Percutaneous cooled-probe microwave versus radiofrequency ablation in early-stage hepatocellular carcinoma: a phase III randomised controlled trial. *Gut*. 66 (6):1172–1173.

Zhong, J.H., Ke, Y., Gong, W.F. et al. (2014). Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg* 260 (2): 329–340.

Zhu, A.X., Finn, R.S., Edeline, J. et al. (2018). Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a nonrandomised, open-label phase 2 trial. *Lancet Oncol* 19: 940–952.

Zimmermann, C., Swami, N., Krzyzanowska, M. et al. (2014). Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet (London, England)* 383 (9930): 1721–1730.

Further Reading

- EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018. Journal of Hepatology.69. 182–236.
- Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for Study of Liver Diseases. Hepatology. 68. 723–750.
- Lubel, J. S., Roberts, S. K., Strasser, S. I., Thompson, A. J., Philip, J., Goodwin, M., Clarke, S., Crawford, D. H., Levy, M. T., & Shackel, N. 2021. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. *The Medical journal of Australia*, *214*(10), 475–483.
- Asia-Pacific Primary Liver Cancer Expert Association Annual Board Meeting Report 2021

19 Management of Metastic Liver Cancer

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The liver is the most common site for blood-borne metastasis from colorectal cancers, and is the dominant metastatic disease site just prior to death (Stewart et al. 2018). Until the early 1980s, it was generally accepted that hepatic metastases from colorectal cancer represented just one site in a wide systemic dissemination of tumor, and partial hepatectomy was rarely used as treatment. Since then, numerous studies have shown that resection can prolong survival and potentially provide cure. Surgical excision for hepatic metastases from colorectal cancer is now considered standard therapy for patients with metastases isolated to the liver. In the next section, we will summarize the data supporting such therapies, as well as clinical parameters that influence outcome. Since acceptance of surgery as a local therapy for this disease, a number of other local therapies have emerged as effective treatment options for hepatic metastases. The data supporting use of ablative, radioembolic, and radiation therapies will also be presented. These tissue-sparing local treatments for hepatic colorectal metastases have further extended treatment possibilities.

Recent advancements in chemotherapies and biologic therapies have also contributed to effective treatment for hepatic colorectal metastases and extended the possibility for cure. Patients previously beyond curative therapies can be converted by systemic therapies to becoming resectable. Those not resectable for cure are effectively treated by systemic and regionally delivered therapies, including hepatic artery infusion pump therapy, to achieve extension of life. In the following sections we will also present the current approach of palliative neoadjuvant, and adjuvant systemic and regional infusion therapies. The combined advances in surgery, systemic and regional infusion therapies, along with radiation, radioembolization, and ablative therapies have transformed this disease from uniformly and immediately fatal to an increasingly curable one.

Surgical Therapy for Colorectal Liver Metastases

Camille Stewart, Felix Ho & Yuman Fong

Introduction

The liver is the most common site for distant metastasis from colorectal cancers. Single institutional studies have suggested that one-quarter of patients will be found to have hepatic metastases synchronous with their colorectal primary, and nearly half of patients will develop metachronous liver metastasis colorectal resection (Ekberg et al. 1987). Specifically for patients presenting with stage IV disease, a recent study based on the SEER database found that 72% of these patients resented with liver metastases at the time of diagnosis (Ituarte et al. 2022). Liver resection, however, is only performed for the minority of these patients (<10%) (Raoof et al. 2019). Untreated colorectal metastasis to the liver uniformly results in death within months (Oxley and Ellis 1969). If liver disease is unresectable, it generally dominates the clinical picture until death; 83% of patients die with liver disease, and 49% of patients have the liver as the dominant metastatic disease at the time of death (Stewart et al. 2018). Even with the best current systemic chemo- and biologic therapies, median survival of unresected disease is less than less than 2.5 years (Cremolini et al. 2020a; Cunningham et al. 2004; Hurwitz et al. 2004; Saltz et al. 2000).

Abundant data accumulated over many decades have definitively demonstrated that partial hepatectomy can be curative treatment for colorectal liver colorectal metastases (Creasy et al. 2018a; Wagner et al. 1984; Wilson and Adson 1976). We will review these data in this chapter. The patient selection criteria, preoperative work-up, and clinical determinants of outcome will be presented in the context of current multimodality treatment. While the bulk of discussion on chemotherapy will be presented in the chapter on systemic and regional therapy for this cancer, we will summarize the issues related to perioperative use of chemotherapy as it relates to surgical outcome and conduct.

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Natural History

Metastatic colorectal cancer has an incidence of 9.8 per 100,000 individuals; patients specifically with liver metastases make up 7.1 per 100,000 (Ituarte et al. 2022). The incidence of metastatic colorectal cancer is higher in males (11.7) and African Americans (14.6) (Ituarte et al. 2022). Many studies in the twentieth century examined the outcome of untreated hepatic colorectal metastases. Median survival is 5–10 months (Table 1). Outcome is clearly related to tumor burden (Bengmark and Hafstrom 1969; Bengtsson et al. 1981; Wood et al. 1976). While the one-year survival was only 5.7% for patients with widespread liver disease, 60% of patients with solitary metastasis were alive at one year and these patients with solitary metastases had a mean survival of 25 months (Wood et al. 1976). Wood et al. compared the survival of 13 unresected patients with technically resectable disease with 100 patients with unresectable disease. For these 13, the 1-, 3-, and 5-year survival was 77%, 23%, and 8%, compared with 15%, 0, and 0 for the unresectable group (Wood et al. 1976). Wagner et al. reported the 3- and 5-year survival for untreated resectable disease to be 14% and 2%, compared with 4% and 0 for unresectable disease (Wagner et al. 1984). Stangl et al. reported six independent determinants of survival in patients with untreated colorectal liver metastases: % liver volume replaced by tumor, grade of malignancy, presences of extrahepatic disease, mesenteric lymph node disease, carcinoembryonic antigen value, and age (Stangl et al. 1994). Regardless of these factors, five-year survival for untreated disease is extremely rare.

Similar conclusions were found in older case-control studies. Wilson and Adson (Wilson and Adson 1976) compared 60 patients with resection to 60 patients with a comparable number of lesions and extent of disease not subjected to resection. The five- and ten-year survivals of resected patients were 25% and 19%, while no unresected patient survived five years. Two other case-control studies had almost identical results (Scheele et al. 1991; Wagner et al. 1984). These data, combined with extensive data documenting long-term survival after hepatectomy, have led to general acceptance of hepatectomy as an effective treatment for liver colorectal metastases, even though no randomized trial comparing systemic therapy alone to surgery with or without systemic therapy has ever been performed.

Results of Resection for Colorectal Liver Metastases

Many studies have been published demonstrating resection of liver metastases from colorectal primaries is safe and effective (Simmonds et al. 2006). Results from retrospective and prospectively gathered data show that even without randomized controlled trial data, hepatectomy is superior to systemic treatment alone (Table 2). The reason is that virtually no one under medical management lives more than five years. A population based study from the California Cancer Registry comparing colorectal liver mastectomy rate and survival by medical service area demonstrated a 24-month survival gain for patient’s whose treatment choices were influenced by rates of resection in their geographic area (Raoof et al. 2019). This translated into increasing survival 105% at 1 year, 223% at 2 years, 375% at 3 years, and 370% at 5 years (Raoof et al. 2019). This study highlights the importance of patient referral to a multidisciplinary team that includes hepatobiliary surgery, since this statistically improves three- and five-year overall survival (Lordan et al. 2009). Further, while African Americans with colorectal liver metastases have a 17% higher hazard of death compared to Caucasian patients, this difference is lost when examining patients who have undergone liver resection for colorectal liver metastases (Thornblade et al. 2020). It should also be noted that disease-specific survival of patients who die of liver metastasis (17.3±1.5 months) is shorter than for those who die of other intra-abdominal disease (29.7±4 months; $p<0.0001$), intrathoracic disease (39.3±5 months; $p<0.0001$), or brain metastasis (35.6±5.3 months; $p<0.0001$). As such,

Table 1 Natural history of liver metastasis from colorectal cancer.

Study	Number of patients	Median (months)	1 yr %	3 yr %	5 yr %
Bengmark 1968 (Bengmark and Hafstrom 1969)	173	–	5.7	0	0
Oxley 1969 (Oxley and Ellis 1969)	640		27	4	1
Wood 1976 (Wood et al. 1976)	113	6.6	15	3	1
Wagner 1984 (Wagner et al. 1984)	252	–	49	7	2
Scheele 1990 (Scheele et al. 1990)	921	–	–	–	0
Stangl 1994 (Stangl et al. 1994)	484	7.5	31	2.6	1

– Data not specified.

Table 2 Results of hepatic resection for metastatic colorectal cancer.

Study	Number of patients	Operative mortality%	1-year survival %	3-year survival %	5-year survival %	10-year survival %	Median months
Kato 2003(Kato et al. 2003)	585		–	–	33	–	–
Mutsaerts 2005 (Mutsaerts et al. 2005)	102	3	–	–	29	–	–
Wei 2006 (Wei et al. 2006)	423	2	93	–	47	28	53
House 2010 (House et al. 2010)	563	0.5		65	43		
Hackl 2014 (Hackl et al. 2014)	374		87		32	18	52
Hallet 2016 (Hallet et al. 2016)	2320				64		
Margonis 2016 (Margonis et al. 2016)	485						
Neal 2017 (Neal et al. 2017)	488	2		48	30		
Sasaki 2018 (Sasaki et al. 2018)	604		94	69	50		62
Margonis 2019 (Margonis et al. 2019)	1099		88	61	42		

– Not specified.

hepatic resection alters not only length of survival but also eventual cause of death, by allowing other, more indolent sites of metastatic disease to become clinically evident and important (Stewart et al. 2018).

Since all major series have demonstrated that hepatectomy results in long-term survival for a proportion of patients, these data are so compelling that randomized trials are both unethical and unnecessary. As safety of hepatectomy has improved, clinicians have been increasingly willing to perform ever more extensive resections and multi-phase operations to eradicate tumor. In addition, as long-term outcomes improve due to improving adjuvant therapies, clinicians have been extending the indications for resection. Following is a review of the perioperative and long-term outcomes.

Perioperative Mortality and Morbidity

In the prior edition of this text published in 2009, the mortality associated with an elective liver resection for colorectal metastases was reported as less than 5%, ranging from 1–7% (Doci et al., 1991; Belli et al. 2002; Busuttil 1974; Choti et al. 2002; Fong et al. 1999; Foster 1978; Hughes et al. 1986; Jamison et al. 1997; Kato et al. 2003; Minagawa et al. 2000; Mutsaerts et al. 2005; Nordlinger et al. 1996; Rosen et al. 1992; Scheele et al. 1995a; Schlag et al. 1990; Wei et al. 2006; Younes et al. 1991) (Table 2). The majority of those deaths were from perioperative hemorrhage, liver failure, or sepsis. In 2010, a cohort of 1,600 was reported from Memorial Sloan Kettering, showing that 30-day mortality decreased from 2% for patients treated from 1985 to 1998 (n=1037) to 0.5% for those treated from 1999 to 2004 (n=563). More recently, 30-day mortality rates were again reported as <1% from the American College of Surgeons NSQIP database from 2014 to 2016 (Wiseman et al. 2019). Mortality was associated with operative time >6 hours, use of the Pringle maneuver, and biliary reconstruction.

Complication rates remain high because of the physiologic stress of removing a significant portion of such a metabolically and immunologically important organ as the liver. A recent meta-analysis of 41 studies performed from 2003 to 2018, including 12,817 patients who underwent surgical resection for colorectal liver metastases reported post-operative complications occurred in 26%, and 19% were grade 3+ (Dorcaratto et al. 2019). The types of complications were not listed. Of note, however, was that patients who experienced a post-operative complication had significantly lower five-year overall (HR 1.43, 95% CI 1.3–1.57) and disease-free survival (HR 1.38, 95% CI 1.27–1.49) (Dorcaratto et al. 2019).

In a study of the American College of Surgeons NSQIP database from 2014 to 2016, morbidity was 33% (Wiseman et al. 2019). In this study, types of complications were detailed; the two most common were blood transfusion within 72 hours (16%), and surgical site infection (10%). Other common complications were readmission (9%), post-operative intervention (8%), bile leak (6%), and post-operative liver failure (5%) (Wiseman et al. 2019). Complications were more likely in patients who underwent open operations, had operations >4 hours, those who underwent major hepatectomy, simultaneous colectomy, and had tumor resection size >5 cm (Wiseman et al. 2019). Peri-operative mortality was 21/2832 (0.7%). Previously, pulmonary complications were a significant source of morbidity for these patients. In 1985, Coppa et al. reported that 5–10% of pleural effusions may be sufficiently symptomatic to require tube thoracostomy (Coppa et al. 1985), and in 1990, Schlag et al. reported that pneumonia occurred in 5–22% (Schlag et al. 1990). The risk of pulmonary complications have now decreased substantially – pneumonia occurs in 3%, failure to wean from the ventilator in 1%, and re-intubation in 2% (Wiseman et al. 2019). Concordant with decreasing complications, length of hospitalization for colorectal liver metastasectomy has also decreased in the United States. We previously reported the usual hospital stay in major centers after a major liver resection is generally less than two weeks (Fong et al. 2005). In contrast, the American College of Surgeons NSQIP database study from 2014 to 2016, the mean length of stay was only 6.3 days, and 95% of patients were discharged home (Wiseman et al. 2019). This may be in part due to a difference in approach that has evolved regarding sparing of parenchyma (discussed in more detail under "Margin Status").

Long-term Outcomes

A number of series now have sufficiently long follow-up for us to be confident that 10-year survival after hepatectomy can be expected in 20–30% of patients (Table 2) (Fong et al. 1999; Minagawa et al. 2000; Wei et al. 2006). In House et al. recurrence free, disease free, and overall survival were compared for patients treated before 1999, and from 1999 to 2004. These authors found that patients with a low clinical risk score (<3) had median disease specific survival before 1999 of 54 months; this increased to 87 months for the later time period (House et al. 2010). Patients with a clinical risk score of 3+, however, had similar median disease specific survival regardless of time period (House et al. 2010). This was similarly shown in a large cohort study from Germany; patients who had <3 colorectal liver metastases and underwent resection had improved 1, 5, and 10-year overall survival compared to those with >3 (Hackl et al. 2014).

Margin Status and Surgical Approach

It is largely believed that margin status impacts long-term oncologic outcomes for patients undergoing resection of colorectal liver metastases. Questions arise here regarding method of resection (anatomic wedge) and oncologic value of microscopic margins (R1 vs R0). Traditionally, anatomic resections were advocated for metastatic colorectal cancer because of the high likelihood of a positive margin for wedge resections, but this is no longer the case. In a classic series from Johannes Scheele, wedge resections were associated with a positive margin rate of 19% (Scheele et al. 1995b). DeMatteo et al. reviewed resected colorectal liver metastases from the Memorial Sloan-Kettering Cancer Center and found that wedge resections had higher rates of margin positivity when compared to anatomic segmental resection (16 vs 8%) (DeMatteo et al. 2000). This translated into a significant difference in median overall survival, favoring those who underwent anatomic resection (38 vs 50 months) (DeMatteo et al. 2000). This was likely due to the difficulty in judging margins of the tumor deep in the parenchyma. Wedge resections are also complicated by the fact that the transection line tends to fracture at the interface of the hard colorectal tumor and soft normal liver. Following the hepatic veins during a segmental resection evolved to assist the surgeon in achieving a negative margin. Later studies showed no difference between wedge and anatomic resections for complications or one, three, and five-year survival (Zorzi et al. 2006). A recent meta-analysis of more than 2500 patients undergoing resection for colorectal liver metastases concluded that both margin status and overall survival were similar between the wedge and anatomic resections (Moris et al. 2017). This is likely due to expertise of surgeons at present for choosing to use either wedge or segmental resections to achieve a low rate of margin positivity.

Regarding how margins should be assessed, Sadot et al. examined 2368 patients who underwent hepatic resection for metastatic colorectal cancer from 1992 to 2012, and found that margin clearance of 1 mm or more was associated with improved overall survival, compared to those with sub-millimeter margin clearance (Sadot et al. 2015). In another smaller case series of 334 patients from 2018, R1 resection again had worse survival compared to those with negative margins (RR 3.2, 95% CI 2.0–5.2), but there was no difference for patients with 0–1 mm margins vs >1 mm margins (Makowiec et al. 2018). R1 vs R0 status was important for patients with and without neoadjuvant chemotherapy treatment (Makowiec et al. 2018), but surprisingly did not affect one- and three-year hepatic recurrence rates (R0 – 38%, 73% vs R1 – 36%, 68%, respectively) (Makowiec et al. 2018). Others have challenged the value/necessity of an R0 resection from an oncologic perspective. While some perform routine frozen margin assessment with re-resection to negative margins if technically feasible (Makowiec et al. 2018), the value of re-resection after identifying an R1 margin on frozen pathology has been questioned. In a cohort of 332 patients, 74% had R0 resection, 18% had an R1 resection, and 7% initially had an R1 resection identified on frozen section that was converted to an R0 resection by removal of additional tissue (Margonis et al. 2015a). In this study, margin status was not associated with disease free survival, overall survival, or incidence of intrahepatic recurrence (Figure 1) (Margonis et al. 2015a). A notable limitation of this study was the sample size, however, making it difficult to detect differences in outcomes between groups (Margonis et al. 2015a). The authors utilize selective frozen margin assessment after rapid gross evaluation of the specimen with our pathology colleagues. Frozen margins are obtained if there is concern for margin involvement on rapid gross assessment. During this time down-time, we place a clean laparotomy pad (or baby laparotomy pad if minimally invasive) in the resected bed to assess for bile leakage after gross and frozen evaluation have been completed.

It should also be noted that minimally invasive surgery is now within the standard of care for many operations, including liver metastasectomy surgery. The Da Vinci robotic surgical system uses technologically sophisticated equipment to facilitate minimally invasive operations with wristed

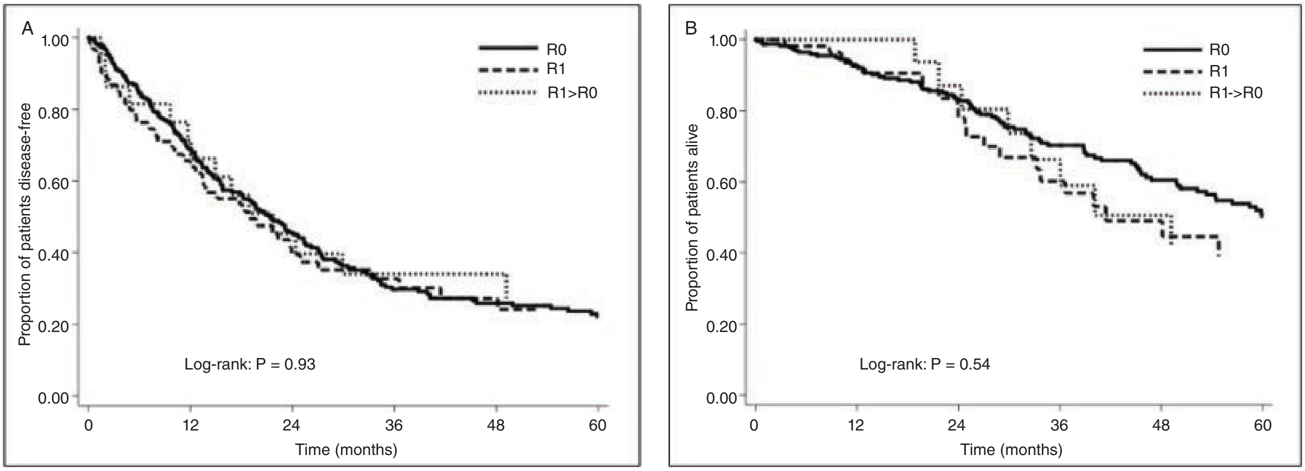


Figure 1 Unadjusted recurrence free (a) and overall (b) survival of patients undergoing hepatic resection for colorectal liver metastases stratified by margin status. Note that margin status was not associated with recurrence free or overall survival on multivariable analyses after adjusting for competing risk factors (Margonis et al. 2015a/Springer Nature).

articulating instruments and three-dimensional visualization. Liver surgery is increasingly being performed with the robotic platform (Lafaro et al. 2020) which has certain advantages over laparoscopic and open surgical techniques. Some of these potential advantages include surgeon ergonomics, enabling a minimally invasive approach for more superior and posterior segment lesions, faster learning curve, superior visualization, and facilitating the use of indocyanine green, and the potential for use of intra-operative liver navigation (Table 3). The patients who are best suited for a minimally invasive approach are those who otherwise would undergo an "incision dominant" open operation, where a large incision is required to remove a small volume of liver parenchyma (Stewart et al. 2021). Our group has reported previously that the majority of patients who undergo minor robotic liver resections have hospitalizations of three days or less (Melstrom et al. 2018) and that patients who undergo minor robotic liver resections have fewer complications and shorter length of stay compared to open operations, resulting in overall lower cost (Stewart et al. 2021). We have previously reported complete descriptions of surgical techniques related to open and minimally invasive techniques for liver metastasectomy, which are beyond the scope of this chapter (Fong and Blumgart 1997; Lafaro et al. 2020). In sum, given the known benefits of minimally invasive surgery, including for liver surgery, and the technical advantages afforded by the robotic surgical system, the authors recommend consideration for a robotic approach in select patients, particularly those planned for minor hepatectomy.

In conclusion, not only is there no doubt that resection prolongs survival in patients with isolated colorectal liver metastases, resection can produce cure from this stage IV cancer. Surgical resection has therefore become standard therapy and treatment of choice for metastatic colorectal cancer isolated to the liver.

Pushing the Limits of Resection

There is a subset of patients anticipated to have an insufficient future liver remnant after removal of all visible hepatic metastatic disease, who may otherwise be good surgical candidates. For these patients, a number of techniques exist to augment the

Table 3 Advantages and limitations of robotic liver surgery (Stewart and Fong 2021/Springer Nature).

Advantages	Limitations
• Surgeon ergonomics	• Inability to palpate the liver
• Enables minimally invasive surgery for superior and posterior liver segment resections	• Increased incision size to remove larger specimens may negate the benefits of smaller initial incisions
• Faster learning curve	• Additional operative time to dock and undock
• Superior visualization, facilitates use of indocyanine green imaging	• Potential for argon gas vascular embolization
• Potential for intra-operative liver navigation	• Increased operative cost

anticipated future liver remnant (FLR) and stave off the dreaded complication of post-hepatectomy liver failure. Some strategies that have been employed for these patients are portal vein embolization (discussed further below), portal vein ligation, two-stage hepatectomy, and more recently Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) (Michal et al. 2020).

Two stage hepatectomy can be employed in patients who present initially with unresectable bilobar disease due to an insufficient future liver remnant. Often, the greater burden of disease is resected first, occasionally with concomitant additional tumor ablation, portal vein ligation, and/or embolization (Lam et al. 2013). The goal is to complete the second stage of the hepatectomy to resect the remaining disease; however, there is a risk of interval disease progression, continued inadequate FLR, portal venous injury/thrombosis, and patient death after the first stage (Lam et al. 2013). In a meta-analysis from 2013, the authors found that 69–92% of patients progressed to the second stage hepatectomy, and that median overall survival for patients after the second stage was 24–44 months (Lam et al. 2013). More recent publications show similar rates of non-completion of the second stage and overall survival (Cunha et al. 2019; Mor et al. 2019). ALPPS is a two-stage hepatectomy variant, initially described in 2011 (Baumgart et al. 2011), intended to induce rapid functional liver remnant hypertrophy, enabling the second stage of the procedure to be performed in 7–14 days (Schnitzbauer et al. 2012). In the first operation of this two-staged technique, segment 4 is completely devascularized by separating the liver parenchyma from the falciform ligament (i.e., liver partition) and the right portal vein is ligated (Torres et al. 2013). Early reports regarding this technique created concern regarding the high morbidity and mortality. Traunt et al. reported on a series of 62 patients who underwent ALPPS from 2011 to 2013, with 40% morbidity, including many with complications after the first stage, and 13% mortality (Truant et al. 2015). An ALPPS Risk Score was developed after examining 528 patients, to facilitate identification of the 9% patients who will have three-month or in-hospital mortality after stage 1 surgery (Linecker et al. 2016). Factors increasing risk before stage 1 of surgery were non-colorectal liver metastases and age >67 years old. Factors increasing risk before stage 2 surgery were complications after stage 1, elevated bilirubin, and elevated creatinine (Linecker et al. 2016). More recently, the LIGRO trial published in 2018 compared ALPPS to usual two-stage hepatectomy with portal vein embolization in 100 non-cirrhotic patients with colorectal liver metastases treated with neoadjuvant chemotherapy and responding or stable disease, requiring liver resection, but not resectable in one step because of a future liver remnant/standardized total liver volume ratio of <30% (Sandström et al. 2018b). They reported a resection rate of 92% in the ALPPS arm compared to 57% in the two-stage hepatectomy arm ($P < 0.0001$) (Sandström et al. 2018b). Of the 48 eligible patients in the ALPPS arm, 41 reached a functional liver remnant (FLR) more than 30% within 7 days, and another 3 reached a FLR more than 30% within 14 days (92%). By comparison, in the two-stage hepatectomy group, 28/49 (57%) of the patients reached 30% FLR without tumor progression; 14 (29%) patients after 7 days, 9 (18%) patients after 4 weeks, and 5 (10%) patients within 7 weeks (Sandström et al. 2018b). The 90-day mortality from the final intervention for patients who completed treatment was 4 (9.1%) in the ALPPS group and 3 (10.7%) in the two-stage hepatectomy group ($P = 0.64$). Thus, mortality from this aggressive approach remains much higher than patients who can undergo resection in a single stage. The authors of the LIGRO trial did report, however, that mortality was limited to patients with a MELD score >9 or an ALPPS risk sore >5 before the second intervention (Sandström et al. 2018b). The first long-term oncologic outcomes from ALPPS were published in 2020, and reported 90-day mortality of 4.9%, median overall survival of 39 months, and recurrence free survival of 15 months (Petrowsky et al. 2020). Therefore, this approach may be considered within the context of a multidisciplinary environment in a high-volume hepatobiliary center with well-selected patients.

Liver transplant for non-resectable colorectal liver metastases has been attempted. In a series of 21 patients with nonresectable colorectal liver metastases treated with liver transplant from 1983 to 1994 at the Medical University of Vienna, 3 patients had genetic and histologically negative lymph nodes and experienced a median overall survival of 118 months (Kappel et al. 2006). In 1991, a series from the University of Cincinnati reported that liver transplant for liver metastases had a 59% recurrence rate (Penn 1991). These authors concluded that liver transplant for metastatic disease generally should not be performed. A prospective pilot study was conducted at Oslo University Hospital to further examine liver transplant in 21 patients with nonresectable colorectal cancer from 2006 to 2011 (Hagness et al. 2013). A third of patients experienced a complication requiring intervention, and metastatic or local recurrence was detected in 19/21 patients after a median of 6 months (Hagness et al. 2013). These authors later compared outcomes of the patients who underwent liver transplant to patients who were treated with FLOX chemotherapy with or without cetuximab in the NORDIC VII trial (Dueland et al. 2015). For patients undergoing liver transplant, the five-year overall survival rate was 56% compared with 9% of patients starting first line chemotherapy, however, patients had similar disease-free survivals of 10 and 8 months, respectively. The potential reason for this discrepancy between disease-free and overall survival was thought by the authors to be a difference in metastatic patterns of relapse and progression (Dueland et al. 2015). Additional randomized trials are underway to further evaluate the utility of liver transplant for nonresectable colorectal liver metastases (Gorgen et al. 2018), but at the time of this writing, transplantation for nonresectable remains outside the standard of care.

Sites of Recurrence and Re-resection

The patterns of recurrence in patients who are not cured by hepatectomy have been well documented (Table 4). Since the liver is a common site for recurrence after hepatectomy, treatment of such recurrences constitutes an important part of the overall treatment plan for patients.

As liver surgeons have become increasingly comfortable with liver resections, an increasing number of repeat hepatectomies are being performed as treatment for recurrent disease. Table 5 summarizes the data for such repeat hepatectomies. These repeat hepatectomies are considered safe, and in many modern series, five-year survival after second resection is reported to be over 40%. The number of patients being treated with repeat hepatectomy has increased over time, survival has been prolonged, and morbidity is lower for these patients than patients undergoing initial hepatic mastectomy, at 11–21% (Andreou et al. 2011; Fukami et al. 2017; Neal et al. 2017). One study further classified these patients into those who had effective salvage therapy, and found that 25% of patients who underwent repeat hepatectomy achieved at least 36 months free of recurrent disease (Butte et al. 2015). While undoubtedly these findings include the effects of selection bias (these patients tend to be younger, have negative margins from their first liver resection, and have smaller tumors (Butte et al. 2015)), they nevertheless demonstrate that repeat hepatectomy can be life-extending when performed on a select cohort of patients.

Prognostic Variables and Scoring Systems

Clinical scoring systems are frequently used for predicting outcomes in medicine. These scoring systems take into account that patient outcomes such as morbidity and mortality are seldom based on a single variable and generally are multi-factorial in

Table 4 Sites of initial recurrence after liver resection for colorectal metastasis.

Study	n	Recurrences	Liver	Liver and other	Lung	Colon/ Rectum
Nordlinger 1987 (Nordlinger et al. 1987)	80	51 (64)	21 (42)	13 (26)	11 (22)	11 (22)
Hohenberger 1990 (Hohenberger et al. 1990)	122	80 (66)	17 (14)	55 (45)	–	–
Hughes 1992 (Maeda et al. 1992)	607	424 (69)	149 (35)	42 (10)	73 (17)	33 (8)
Suzuki (Suzuki et al. 1997)	64	45 (70)	31 (48)	–	16 (25)	–
Butte 2015 (Butte et al. 2015)	952	594 (62)	157 (26)		167 (28)	9 (2)
Hallet 2016 (Hallet et al. 2016)	2320	1099 (47)	473 (43)	225 (20)	176 (16)	
Fukami 2017 (Fukami et al. 2017)	282	193 (68)	78 (40)		47 (25)	
Neal 2017 (Neal et al. 2017)	488	338 (69)	152 (31)	231 (47)		
Gagniere 2020 (Gagnière et al. 2020)	1467	821 (56)	222 (27)	376 (46)	220 (27)	
Takamoto 2020 (Takamoto et al. 2020)	296	247	112 (45)			

n = number of patients (%).

Table 5 Results of repeat hepatic resections.

Author	Resected	Mortality	2-year survival	5-year survival
Elias 1993 (Elias et al. 1993)	28	1 (4)	30	–
Fong 1994 (Fong et al. 1994)	25	0 (0)	30	–
Yamamoto 1999 (Yamamoto et al. 1999)	75	0 (0)	–	23
Muratore 2001 (Muratore et al. 2001)	29	1 (3)	–	–
Suzuki 2001 (Suzuki et al. 2001)	26	0 (0)	–	31
Petrowsky 2002 (Petrowsky et al. 2002)	126	2 (2)	–	43
Shaw 2006 (Shaw et al. 2006)	66	1 (2)	–	44
Andreou 2011 (Andreou et al. 2011)	43	0 (0)		73
Butte 2015 (Butte et al. 2015)	160			65
Fukami 2017 (Fukami et al. 2017)	62	2 (5)		
Neal 2017 (Neal et al. 2017)	71	0 (0)		48
Takamoto 2020 (Takamoto et al. 2020)	122	0 (0)		51

– Data not specified.

nature. While physicians may have a working knowledge of positive or negative influences on the outcomes, understanding the most important variables and assessing the weight of these variables in patients can be difficult. For the surgeon, challenges arise when determining who should be offered an operation and also when providing information regarding prognosis, especially when patients are perceived to possess both favorable and poor prognostic features. Beyond risk stratification, clinical scoring systems importantly facilitate communication between physicians and assist in patient selection for participation in clinical research. As surgeons continue to push the limits of their technical ability, the question "can an operation be done?" shifts to "should an operation be done?" Patients with colorectal cancer liver metastases openly lend themselves to this type of stratification, since a percentage of these patients will be cured with surgery, whereas a percentage will likely incur little or no benefit (Stewart and Fong 2020). The traditional TNM staging systems classifies all patients with colorectal liver metastases in the same category: stage IV. Clearly, however, the patient with a solitary metastasis found four years after resection of a node-negative primary is very different from a patient found with bilobar multiple metastases synchronous to discovery of a node-positive primary.

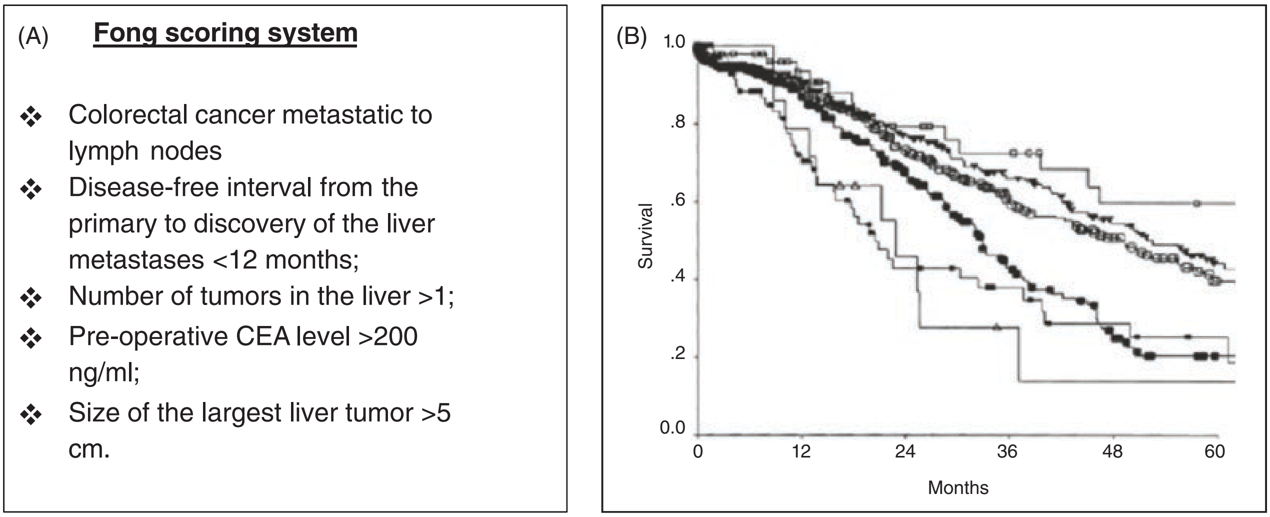
Prognostic Factors

The stage of the primary is a major determinant of outcome; in particular, regional nodal positivity is a powerful predictor of recurrence (Fong et al. 1999; Hughes et al. 1989; Nordlinger et al. 1996; Scheele et al. 1995a). Synchronous presentation of liver metastases also predicts poor outcome (Ballantyne and Quin 1993). Further, patients with right sided colonic primary tumors have shorter median recurrence free survival compared to those with tumors on the left (1.3 vs 1.7 years) and shorter median overall survival (3.6 vs 5.2 years) (Creasy et al. 2018b). Short disease-free interval between primary cancer and hepatic metastases is associated with poor outcome (Hughes et al. 1986; Rosen et al. 1992). Other parameters associated with poor outcome include large size of tumor (Hughes et al. 1986; Stephenson et al. 1988), multiple tumors (Hughes et al. 1986; Rosen et al. 1992), bilateral tumors (Hughes et al. 1986; Rosen et al. 1992), and high carcinoembryonic antigen (CEA) levels (Hughes et al. 1986; Rosen et al. 1992). As mentioned earlier, margin status also plays a role in the oncologic outcome after metastasectomy.

KRAS, NRAS, and BRAF mutational testing has become important in the assessment of metastatic colorectal cancer, since they serve as biomarkers for response to anti-EGFR inhibitors (Douillard et al. 2013; Lievre et al. 2006). They also serve prognostically for patients with colorectal liver metastases undergoing resection. A meta-analysis of 11 studies and 1833 patients with colorectal liver metastases who underwent complete liver resection found that KRAS mutation and BRAF mutation were associated with statistically shorter overall survival (Lievre et al. 2006; Tosi et al. 2017). KRAS mutations were found in 14–46% of patients, whereas BRAF was only identified in 2% of patients (Tosi et al. 2017). The largest study included in this meta-analysis included 334 patients, and showed that KRAS mutation, lymph node metastases, CEA >30 ng/ml, and ablation were all independently associated with decreased overall survival in this patient population (Margonis et al. 2015b). KRAS mutant status is associated with more frequent micro-metastases and positive margins after resection (Zhang et al. 2020). Another systematic review of 78 studies including all patients with colorectal liver metastases and details on KRAS, BRAF, PI3K, and TP53 was performed in 2018 (Tsilimigras et al. 2018). In this study, KRAS mutations were identified in 25–52% of patients. A study of 4124 patents who underwent hepatectomy for colorectal liver metastases found that BRAF mutations were present in 35 (2%) of the patients (Gagnière et al. 2020). These patients more often had multiple synchronous tumors, and had a significantly lower median recurrence free survival (10 vs 22 months, $p<0.001$), and overall survival (40 months vs 81 months, $p<0.001$) (Gagnière et al. 2020). It has also been reported that KRAS mutant circulating cell-free tumor DNA is associated with shorter overall survival, and that the combination of high (>3.33%) KRAS mutant cell-free tumor DNA with CEA >4.5 ug/L best predicted shorter overall survival after surgery (Polivka et al. 2020). Of note, there is a proportion of patients with KRAS mutation discordance; one study reported 15.9% of patients had discordant KRAS testing of the colorectal primary and liver metastases (Ardito et al. 2021). Discordance can occur both in patients with KRAS mutant and wild type colorectal tumors (Ardito et al. 2021).

Scoring Systems

We recently reviewed scoring systems for colorectal liver metastases (Stewart and Fong 2020). The time frame of patients used to develop these scoring systems ranges from 1960 to 2016. Throughout this time the management of these patients has changed significantly, however, most notably with the advent of "modern" chemotherapy options, including irinotecan, first approved in 2000, and oxaliplatin approved in 2002. These combinations of treatments doubled median overall survival for metastatic colorectal cancer from 10 to 20 months (Kelly and Goldberg 2005). Antibody therapies including drugs that target vascular endothelial growth factor (VEGF), such as bevacizumab, and the epidermal growth factor receptor (EGFR) pathway, such as cetuximab, came in the 2000s–2010s. Further, immune checkpoint inhibitors such as pembrolizumab have subsequently become used in patients with microsatellite instability. The biological features which are indications for use of these newer drugs have known prognostic implications on their own (Wu 2018), as


(A) **Fong scoring system**

- Colorectal cancer metastatic to lymph nodes
- Disease-free interval from the primary to discovery of the liver metastases <12 months;
- Number of tumors in the liver >1;
- Pre-operative CEA level >200 ng/ml;
- Size of the largest liver tumor >5 cm.

Figure 2 Fong Clinical Scoring System. Scoring system variables (A) and overall survival curve demonstrating stratification between groups (B) in Fong et al. (1999)/Wolters Kluwer Health, Inc..

described in more detail below, thus significantly impacting outcomes for these patients. The most common variables included in scoring systems for predicting outcome after resection of colorectal liver metastases are pre-operative laboratory values (often CEA), tumor size, number of tumors, nodal status of the primary colorectal tumor, and disease free interval (Stewart and Fong 2020). These factors are all taken into consideration with the Fong Clinical Risk Score (Figure 2), a frequently cited scoring system created in 1999 by Fong et al., utilizing data of 1001 patients treated from 1985 to 1999 at the Memorial Sloan-Kettering Cancer Center (Fong et al. 1999). In this study, there was a 2.8% perioperative mortality rate, and the five-year survival after liver resection was 37%. The authors performed regression analyses to identify features that correlated with disease-free and overall survival, resulting in the selection of five clinical criteria, each getting one point: positive colorectal lymph nodes, disease-free interval < 12 months, number and size of liver tumors, and preoperative CEA level. When this scoring system was applied, the five-year survival correlation coefficient was $r^2 = 0.92$; patients with 0 points had a five-year survival of 60%, compared to 14% for patients with 5/5 points (Fong et al. 1999). This score was superior to prediction based on a number of tumors alone and was considered more practical than scores created by other authors, since all criteria could generally be known prior to surgery (excluding patients with planned synchronous resections). Other factors have since been considered for inclusion in similar scoring systems, including KRAS/NRAS status, progressive or stable disease according to RECIST criteria, presence of extra-hepatic disease, tumor differentiation, location of primary tumor, T-stage of primary tumor, and presence of bilobar tumors, have all been included in various scoring systems (Stewart and Fong 2020).

Neoadjuvant Use of Chemotherapy

Systemic therapies are an important part of the treatment plan for patients with colorectal liver metastases and are further described in the following section of this chapter from the medical oncologist's perspective. It should be acknowledged, however, that in patients who are considered potential surgical candidates, the surgeon plays a critical role in determining the timing of systemic therapy. Further, chemotherapy can affect the quality and function of the liver, which may also be a factor when considering surgery. Thus, the following data are presented for consideration when surgery may be offered.

In a cohort study from Memorial Sloan Kettering from 1999 to 2004, 66% of patients received neoadjuvant chemotherapy, and 65% received adjuvant chemotherapy (House et al. 2010). In a cohort study from Johns Hopkins from 2003 to 2015, 79% of patients received neoadjuvant chemotherapy and 35% also received a biologic agent (Margonis et al. 2016). This trend has persisted since then; in a study of the American College of Surgeons NSQIP database from 2014 to 2016, 60% of patients who underwent partial hepatectomy for colorectal liver metastases received neoadjuvant chemotherapy (Wiseman et al. 2019). Thus, use of chemotherapy prior to liver resection for colorectal liver metastases is used quite commonly. Neoadjuvant chemotherapy may be used to treat occult metastases, test tumor biology, and has been shown to improve progression free survival, but remains a subject of significant debate in patients with up-front resectable isolated liver metastases. In a randomized controlled trial accruing from 2000 to 2004, Nordlinger et al. compared peri-operative chemotherapy (six cycles of FOLFOX4 before and six cycles after) with partial hepatectomy to partial hepatectomy alone for patients with 1–4 colorectal liver metastases (Nordlinger et al. 2008). The initial report, published in 2008, found an improvement in per protocol three-year progression free survival in the peri-operative chemotherapy group (36% vs 8%, p = 0.04) (Nordlinger et al. 2008). Of the 182 patients initially randomized to peri-operative chemotherapy, 40% had a partial response, 38% had stable disease, and 7% had progression of disease (Nordlinger et al. 2008). The final report published in 2013, however, demonstrated no difference in five-year overall survival (51% in the perioperative chemotherapy group, 49% in the surgery only group) (Figure 3) (Nordlinger et al. 2013). The CHARISMA trial (ClinicalTrials.gov ID NCT04513457) which enrolled 967 patients from 2010 to 2020, is comparing the outcomes of neoadjuvant oxaliplatin-based chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable isolated colorectal liver metastases (Van Der Stok et al. 2016). Results of this study have yet to be published. The approach we recommend is a selective use of neoadjuvant chemotherapy. For patients with a high risk of recurrence, such as those with a high clinical risk score (discussed in more detail below), particularly patients with synchronous disease, and those with a lymph-node positive primary, neoadjuvant therapy can also be justified.

In comparison to patients who present with isolated resectable liver metastases, there is a clear role for using chemotherapy in patients with initially unresectable disease to facilitate potential R0 resection in the future. In the FIRE-3 trial, patients with unresectable RAS wild type metastatic colorectal cancer were randomized to FOLFIRI with either cetuximab or bevacizumab; in a subgroup analysis of patients liver limited disease, 29/133 (22%) patients underwent hepatic resection with curative intent with a median overall survival of 56 months (Holch et al. 2018), which was significantly longer than patients who did not undergo hepatic resection (HR 0.55, p = 0.03) (Holch et al. 2018). In a similar study, the CRYSTAL randomized controlled trial compared FOLFIRI ± cetuximab in patients with RAS wild type metastatic colorectal cancer; 10/89 (11%) with liver limited disease ultimately underwent R0 resection (Köhne et al. 2016). In the CELIM trial, patients with either technically unresectable or >5 colorectal liver metastases were randomized to cetuximab with FOLFOX6 or FOLFIRI. In this study, resectability rates increased from 22/68 (32%) at baseline to 41/68 (60%) after receipt of chemotherapy, and 49/106 (46%) patients ultimately underwent R0 resection or R1 and/or ablation (Folprecht et al. 2010). In this study, assessment of resectability was evaluated by seven participating surgeons, and agreement amongst all seven surgeons occurred in only 65% of decisions (Folprecht et al. 2010). Thus, indications to proceed with hepatic resection in these types of patients is nuanced and subject to debate, highlighting the importance of a multi-disciplinary discussion (Folprecht et al. 2010).

Chemotherapy-Associated Liver Injury (CALI)

While the advent of more effective chemotherapy regimens has increased the number of patients with hepatic colorectal metastases who are eligible for curative-intent surgical resection, multiple chemotherapeutic agents have been found to cause histopathologic hepatic changes ranging from steatosis to more severe steatohepatitis, sinusoidal injury, and nodular regenerative hyperplasia. The types chemotherapy-associated liver

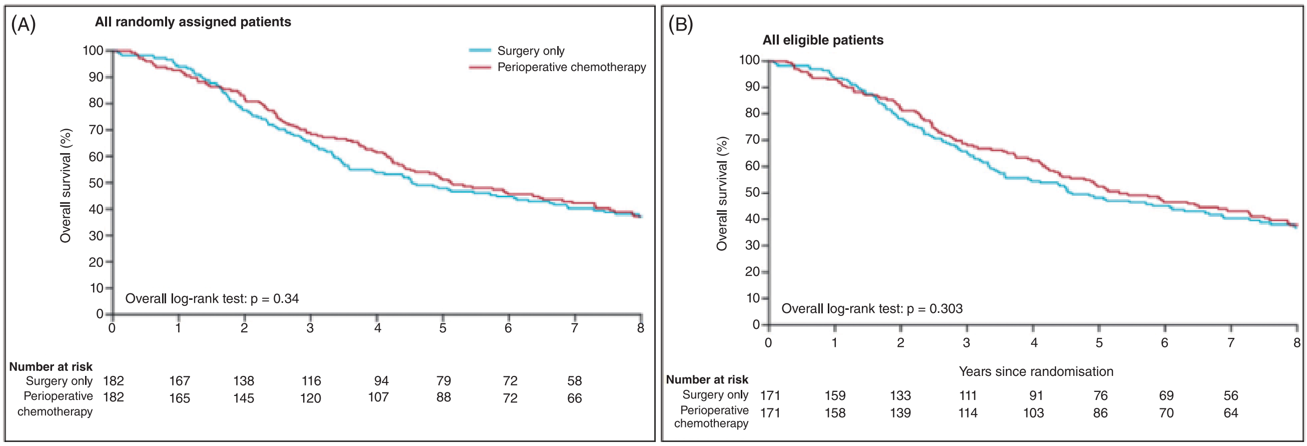


Figure 3 Kaplan-Meier curves of overall survival in all randomly assigned patients (A) and all eligible patients (B) per treatment group of patients with 1–4 colorectal liver metastases. Peri-operative chemotherapy = six cycles of FOLFOX4 before and six cycles after partial hepatectomy. Surgery only = Partial hepatectomy alone. Adapted from Nordlinger et al. (Nordlinger et al. 2008, 2013).

injury (CALI) have varying effects on postoperative morbidity and mortality and appear to be regimen specific. Clinical features include hepatic fatty infiltration and splenomegaly from portal hypertension, which can both be recognized on preoperative axial imaging, and refractory thrombocytopenia (Figure 4). The damage can progress to fibrosis and cirrhosis of the liver. The thrombocytopenia is consumptive and not related to bone marrow suppression. Therefore, it is not corrected even when chemotherapy is stopped.

Steatosis is characterized by accumulation of fat in hepatocytes, while steatohepatitis consists of steatosis associated with inflammatory foci and enlargement (ballooning) of hepatocytes (Kleiner et al. 2005). Whereas 5-FU has been associated with steatosis, which that is generally considered less clinically significant, irinotecan has been linked to steatohepatitis which is associated with increased rates of postoperative liver insufficiency and mortality. In a study of 248 patients receiving preoperative chemotherapy followed by resection of colorectal liver metastases, 20% of patients who received irinotecan were found to have steatohepatitis. Patients with steatohepatitis had significantly higher 90-day mortality compared with patients without steatohepatitis (14.7% v 1.6%, OR=10.5, P = .001) (Vauthey et al. 2006). A systematic review and meta-analysis by the international CALI consortium found that severe steatosis was not significantly associated with postoperative overall or major morbidity but was related to a decreased rate of liver surgery-specific complications (OR 0.52, p = .05). In contrast, patients with steatohepatitis had increased rate of postoperative liver surgery-specific complications (OR 2.08, p = .012) (Zhao et al. 2017).

Oxaliplatin is associated with sinusoidal obstruction syndrome (SOS), which has been associated with perioperative morbidity and encompasses several different histopathologic lesions including sinusoidal dilatation, nodular regenerative hyperplasia (NRH), peliosis, and centrilobular fibrosis (Rubbia-Brandt et al. 2010; Soubrane et al. 2010). Among these, NRH is of particular concern given its increased risk of postoperative liver failure and portal hypertension (Viganò et al. 2015). In a study of 406 patients undergoing liver resection after chemotherapy between 2000 and 2012, NRH was identified in 87/406 (21%) of patients, and was more often found in patients after treatment with oxaliplatin (21% vs. 8%, p = 0.003). NRH was an also independent predictor of postoperative liver failure (9% with NRH vs. 2% without, p = .02), especially those with higher grades of NRH (grade 2 – 14.3%; grade 3 – 25%) after major hepatectomy (Viganò et al. 2015). Conversely, the addition of bevacizumab to oxaliplatin appears decrease both incidence and severity of SOS and NRH (Ribero et al. 2007b; Rubbia-Brandt et al. 2010; Viganò et al. 2015). Rubbia-Brandt et al. found that in 274 patients who underwent resection of colorectal liver metastases after oxaliplatin therapy, 54% had moderate/severe SOS, 25% developing NRH. In patients treated with oxaliplatin and bevacizumab the incidence of moderate/severe SOS and NRH were both significantly lower (31% vs. 62%, p<0.01; 11% vs. 29%, p<0.01, respectively) (Rubbia-Brandt et al. 2010).

The impact of the number of neoadjuvant chemotherapy cycles on liver regeneration remains unclear. While some studies have described lower regeneration rates after more than six cycles of treatment, other studies have not found such

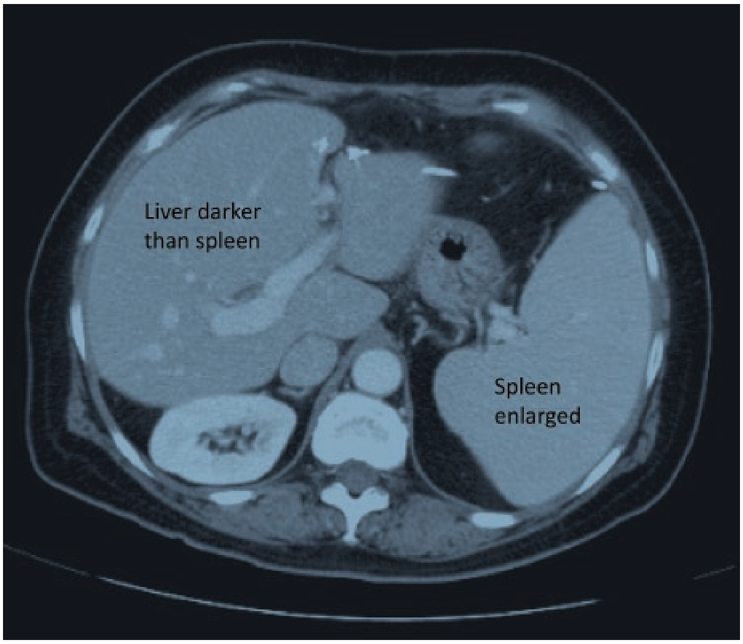


Figure 4 Typical radiologic findings for chemotherapy-associated steatohepatitis. CT of the abdomen demonstrates steatosis of the liver as indicated by the liver being darker than the spleen. Splenomegaly is also seen. The third part of the triad that characterizes this syndrome is a thrombocytopenia due to increased clearance of platelets by the spleen.

differences. Another consideration is the time interval between completion of chemotherapy and hepatic resection and the types of chemotherapy, as mentioned earlier. Many patients subjected to second- and third-line therapies remain candidates for liver resection, whereas in years past, most patients failing first-line therapy were unlikely to be offered surgery. Thus, CALI has become increasingly more commonplace, and therefore is important to recognize.

Portal Vein Embolization and Preoperative Imaging

The development of CALI is not purely academic, as it may lead to additional interventions including preoperative portal vein embolization (PVE) to grow the future liver remnant (FLR) before resection. PVE is discussed in more detail under the Interventional Radiology section of this chapter but is reviewed here in brief here from the surgeon's perspective, along with data related to pre-operative imaging.

Originally, clinicians suggested using PVE when the planned remnant liver after resection was less than 25% of total functional liver (Hemming et al. 2003). The safe cut-off for major hepatectomy was then moved to 20% future liver remnant for patients with otherwise normal livers that had not been exposed to chemotherapy (Kishi et al. 2009). Shindoh et al. later reported on a series of 194 patients undergoing major hepatectomy and found that pre-operative chemotherapy beyond 12 weeks was significantly associated with post-hepatectomy liver insufficiency (Shindoh et al. 2013c). In patients with an FLR less than 30%, post-hepatectomy liver insufficiency occurred in only two patients, both with chemotherapy durations more than 12 weeks, but all patients with a FLR greater than 30% survived (Shindoh et al. 2013c). Thus, at this time cut-off values of 20% FLR for otherwise normal livers, and 30% FLR for livers exposed to chemotherapy are generally used when considering major hepatectomy and the risk of post-hepatectomy liver insufficiency and failure. Degree of hypertrophy and growth rates after PVE also serve as predictors of outcome after major hepatectomy (Leung et al. 2014). This was demonstrated by Leung et al., who reported that no patients in their series of 153 patients experienced liver failure when growth rate was greater than 2.66%/week (Leung et al. 2014). Low growth rates however were highly predictive of post-hepatectomy liver failure.

Pre-operative imaging is critical to any discussion regarding assessment of FLR since the goal of surgical intervention is to address known metastatic disease. While practice varies, the evidence suggests that the best methods for detection of colorectal liver metastases are contrast enhanced multi-phase computed tomography (CT) scan and magnetic resonance imaging (MRI). Current generation helical CT with contrast enhancement of vasculature is invaluable in determining number of lesions, relationship to lesions of vascular structures, and potential involvement of neighboring organs. MRI, however, has been shown to be more sensitive than CT for lesions smaller than 10 mm (Niekel et al. 2010). Further, contrast agents such as gadoxetic acid are increasingly being used to identify metastatic lesions. Gadoxetic acid (marketed as EOVIST in the United States (Eovist (gadoxetate disodium) solution label – Accessdata.fda.gov 2010)) is taken up by hepatocytes, allowing combined dynamic imaging and hepatocyte-specific imaging in one examination (Zech et al. 2007). Sensitivity for identifying colorectal liver lesions using gadoxetate contrast enhanced MRI has been reported to be 90–95% vs 72–75% for multi-phase contrast enhanced CT scan (Granata et al. 2019). The CAMINO study is an international multicenter prospective study evaluating whether MRI has sufficient clinical added value to be routinely added to CT in the staging of CRLM (Görgec et al. 2021). At this time, in our practice, we generally obtain both contrast enhanced CT and MRI pre-operatively given the value of both imaging modalities.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) exploits the glucose-avid nature of colorectal cancers to image tumors. It was previously reported patients with hepatic colorectal metastases who were assessed by FDG-PET prior to liver resection had higher resectability, lower recurrence, and improved long-term survival (Strasberg et al. 2001) because of its ability to detection of extrahepatic disease, such as nodal, peritoneal, lung, or bone metastases. It is inferior to CT or MRI for detection of liver lesions because the normal liver is also a glucose-avid tissue and therefore the background is often too high (Akhurst et al. 2005).

Key Take Home Messages

- All patients with colorectal liver metastases should be evaluated by a surgical team within the context of a multidisciplinary environment.
- Resection of colorectal liver metastases is the standard of care for patients with resectable disease since it prolongs survival and has the potential for cure.
- Parenchymal sparing and minimally invasive approaches are appropriate for colorectal liver metastasectomy.
- Strategies including portal vein embolization and two-stage hepatectomy can be employed for initially inadequate future liver remnant.

Areas for Further Research

- Timing of systemic therapy for patients who present with resectable colorectal liver metastases is subject to debate.
- Pushing the limits of resection with high-risk procedures, such as Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) is subject to debate.

Trusted Links for Further Reading

- Stewart CL, Warner S, Ito K, et al. Cytoreduction for colorectal metastases: liver, lung, peritoneum, lymph nodes, bone, brain. When does it palliate, prolong survival, and potentially cure? Curr Probl Surg. 2018 Sep;55(9):330–379. doi: 10.1067/j.cpsurg.2018.08.004. Epub 2018 Oct 4. PMID: 30526930; PMCID: PMC6422355.
- Raoof M, Haye S, Ituarte PHG, Fong Y. Liver Resection Improves Survival in Colorectal Cancer Patients: Causal-effects from Population-level Instrumental Variable Analysis. Ann Surg. Oct 2019;270(4):692–700. doi:10.1097/sla.0000000000003485
- Margonis GA, Buettner S, Andreatos N, et al. Prognostic Factors Change over Time after Hepatectomy for Colorectal Liver Metastases: A Multi-institutional, International Analysis of 1099 Patients. Ann Surg. 2019 Jun;269(6):1129–1137. doi: 10.1097/SLA.0000000000002664. PMID: 31082912.
- Nordlinger B, Sorbye H, Glimelius B, et al; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomized, controlled, phase 3 trial. Lancet Oncol. 2013 Nov;14(12):1208–15. doi: 10.1016/S1470-2045(13)70447–9. Epub 2013 Oct 11. PMID: 24120480.
- Melstrom LG, Warner SG, Woo Y, et al. Selecting incision-dominant cases for robotic liver resection: towards outpatient hepatectomy with rapid recovery. HepatoBiliary Surgery and Nutrition. 2018–04-01 2018;7(2):77–84. doi:10.21037/hbsn.2017.05.05

Systemic Chemotherapy

S. Lindsey Davis

First-line Therapy for Metastatic Disease

For nearly four decades the treatment of choice for colorectal cancer was fluorouracil (5-FU) and leucovorin (LV). The average response rate was 20% and the average median survival was 12 months (Saltz et al. 2000). In the 1980s, a topoisomerase inhibitor, irinotecan, demonstrated tumor responses in pretreated patients with colorectal cancer. Then a study comparing 5-FU with or without irinotecan in chemotherapy-naïve patients reported higher response rates and a significant survival advantage for the irinotecan-containing regimen (Douillard et al. 2000; Rougier et al. 1998). In this study, a continuous infusion 5-FU with LV and irinotecan was associated with a median survival of 17 months with the three-drug combination vs 14.1 months with 5-FU / LV alone (Douillard et al. 2000).

The next drug to show activity in treating colorectal cancer was oxaliplatin. Infusion of 5-FU and LV combined with oxaliplatin (FOLFOX) as first-line therapy produced response rates of approximately 50% (de Gramont et al. 2000; Giacchetti et al. 2000). In an intergroup phase III trial (Goldberg et al. 2004), metastatic colorectal cancer patients were randomized to FOLFOX versus bolus irinotecan/5-FU/LV (IFL). The study demonstrated a significant increase in response rate, time to progression and median survival for FOLFOX versus IFL with 45% responding to FOLFOX with a 19.5 month median survival (Goldberg et al. 2004).

The order in which these regimens should be administered remains unclear. In the Tournigand study, FOLFOX followed by FOLFIRI (infusional of 5-FU/LV/irinotecan) compared to FOLFIRI followed by FOLFOX produced similar median survivals of 21.5 and 20.6 months, respectively (Tournigand et al. 2004). Similarly, a phase III study evaluating FOLFIRI versus FOLFOX4 in the first line setting was associated with similar overall response rates, median time to progression, and overall survival (Colucci et al. 2005).

Oral capecitabine has also been evaluated as substitute for infusional 5-FU in combination with oxaliplatin in the treatment of metastatic colorectal cancer. Multiple studies have confirmed comparable efficacy between the CAPOX and FOLFOX regimens, though potential for increased toxicity with capecitabine (Guo et al. 2016). This is especially true in the US population related to regional differences in capecitabine tolerability (Haller et al. 2008). The efficacy of the combination of oral capecitabine and irinotecan as compared to the FOLFIRI regimen has been shown to be similar in a number of clinical trials (Guo et al. 2014). However, in the US population this combination was associated with a significant increase in toxicity and decrease in PFS as compared to FOLFIRI (5.8 vs 7.6 months; $p = 0.015$) (Fuchs et al. 2007).

Triplet combination therapy of 5-FU, oxaliplatin and leucovorin in the FOLFOXIRI regimen has also been compared to two-drug regimens with 5-FU and oxaliplatin or irinotecan. The majority of these trials are associated with favorable progression free and overall survival results in the FOLFOXIRI arm, at the expense of increased rates of high-grade toxicity (Cremolini et al. 2020b).

The addition of biologic agents targeting vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) to first-line chemotherapy regimens has led to further improvement in survival outcomes. Anti-EGFR monoclonal antibodies cetuximab and panitumumab are effective in patients with *RAS* wild-type tumors, but not those with *RAS* mutations (*KRAS* exon 2, 3, 4 or *NRAS* exon 2, 3, 4) (Sorich et al. 2015). Increasingly, the site of origin of the primary tumor is being recognized as an additional predictor of response within the *RAS* wild-type population. The phase III CALGB/SWOG 80405 trial demonstrated an increased overall survival in patients with *RAS* wild-type left-sided primary tumors (originating in the splenic flexure to rectum) treated with cetuximab rather than bevacizumab (39.3 vs 32.6 months, HR 0.77), but improved survival in patients with right-sided primary tumors (originating in the cecum to the hepatic flexure) treated with first-line bevacizumab as compared to first-line cetuximab (29.2 vs 13.6 months, HR 1.36) (Venook et al. 2016). The underlying mechanism of this "sidedness" is being further explored but thought related to the varied molecular characteristics of colorectal cancers across primary disease sites.

For those patients with *RAS* mutant tumors or *RAS* wild-type tumors originating in the right side of the colon, bevacizumab is the targeted therapy of choice. The benefit of bevacizumab was first documented in combination with the IFL regimen, with improved response rate (45% vs 35%) and overall survival (20 vs 16 months). However, with more modern chemotherapy backbone regimens these improvements have not been as pronounced, as demonstrated in a pooled analysis of bevacizumab trials which documented overall survival of 19.8 vs 17.6 months in patients receiving regimens with and without bevacizumab (Hurwitz et al. 2013). In addition, the increased risk of bleeding, clotting, and impaired wound healing related to bevacizumab must be considered with this agent.

Two trials have demonstrated that simultaneous addition of both EGFR and VEGF targeted therapies to cytotoxic chemotherapy regimens is associated with inferior progression free survival, and thus these combinations are not recommended, even in a *RAS* wild-type population (Tol et al. 2009) (Hecht et al. 2009).

In the small subset of patients (3–6%) with metastatic colorectal cancer who have deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) tumors, the first-line treatment of choice is immune checkpoint inhibitor therapy rather than cytotoxic chemotherapy regimens. This is based on results from the KEYNOTE-177 trial demonstrating improved progression free survival (16.5 vs 8.2 months) with PD-1 inhibitor pembrolizumab vs chemotherapy with an oxaliplatin- or irinotecan-containing regimen in this population (Andre et al. 2020).

Later-line Therapy for Metastatic Disease

Options for additional therapy following progression on a first-line regimen depend on the initial regimen, as well as molecular characteristics of the tumor (Table 6). For those patients who received an oxaliplatin-based regimen up-front, an irinotecan-based regimen is typically selected, and vice versa (Tournigand et al. 2004). For those treated with FOLFOXIRI, the best second-line chemotherapy regimen is not established, but addition of a VEGF or EGFR inhibitor may be considered in combination with cytotoxic chemotherapy according to the targeted therapy utilized in the first line setting and *RAS* mutation status.

In this population, as well as those who have progressed on separate oxaliplatin- and irinotecan-based regimens, both multi-kinase inhibitor regorafenib and trifluridine-tipiracil are also options for treatment. Regorafenib was associated with a modest, though statistically significant improvement in overall survival as compared to best supportive care (6.4 vs 5 months, HR 0.77) in the CORRECT trial (Grothey et al. 2013). Similarly, trifluridine-tipiracil was associated with a statistically significant increase in overall survival of 7.1 vs 5.3 months with best supportive care (HR 0.68) (Mayer et al. 2015). Subsequently, trifluridine-tipiracil has been combined with bevacizumab with an improved overall survival of the combination vs trifluridine-tipiracil alone (9.4 vs 6.7 months, HR 0.55) (Pfeiffer et al. 2020).

Additional therapies have shown benefit for patients with particular molecular characteristics beyond the first-line setting. For patients with *RAS* wild-type, *BRAF* V600E mutant disease, the combination of cetuximab plus encorafenib provides improved overall survival of 9.3 vs 5.9 months in patients treated with irinotecan or FOLFIRI plus cetuximab (HR 0.61). In patients with *RAS* wild-type disease that is human epidermal growth factor receptor 2 (HER2) positive, trastuzumab plus lapatinib, or pertuzumab may be considered based on data from the HERACLES (Sartore-Bianchi et al. 2016) and MyPathway studies (Meric-Bernstam et al. 2021). For the rare patient with tropomyosin receptor kinase

Table 6 Molecular targeted therapies for the treatment of metastatic colorectal cancer.

Regimen	Line of therapy	Molecular alteration	Incidence in colorectal cancer
Cetuximab Panitumumab	First line and beyond	*RAS* Wild type	50–70%
Cetuximab/encorafenib	Second line and beyond	*BRAF* V600E mutant	3–10%
Pembrolizumab	First line and beyond	MSI high, dMMR	3–6%
Trastuzumab/lapatinib Trastuzumab/pertuzumab	Second line and beyond	HER2 overexpression	3–5%
Larotrectinib Entrectinib	Second line and beyond	*NTRK* fusion	0.5–1%

(TRK) fusion-positive disease (0.5–1%), TRK inhibitors including larotrectinib and entrectinib are favored following first-line treatment (Demetri et al. 2022; Hong et al. 2020). These treatment options demonstrate the importance of broad testing of tumor for somatic mutations in all patients with metastatic colorectal cancer.

Systemic Therapy for Patients with Initially Unresectable Hepatic Metastases

In patients with liver-limited metastatic disease for whom surgical resection is not initially feasible, systemic therapy is typically recommended to help downstage disease, as well as to assess the biology of the metastatic cancer. The benefit of one cytotoxic regimen over another has not been proven in this setting. The higher response rates associated with FOLFOXIRI make this a consideration for a patient population able to tolerate the toxicity of this regimen. Data from a pooled analysis of trials evaluating the FOLFOXIRI/bevacizumab regimen in the setting of initially unresectable hepatic metastatic disease demonstrated an overall response rate of 69%, which led to surgical conversion in 39.1% of patients and R0 resection in 28.1% (Tomasello et al. 2017).

The role of biologic targeted therapies in combination with cytotoxic regimens is also not well-defined in this setting. Minimal improvement in resectability rate, from 6.1% with oxaliplatin-based chemotherapy alone to 8.4% with the addition of bevacizumab, was demonstrated in a randomized trial of 1401 patients with unresectable hepatic metastases (Saltz et al. 2008). However, in a randomized trial of patients with *RAS* mutant metastatic colorectal cancer, patients who received FOLFOX/bevacizumab had a higher objective response rate of 55% as compared to 37% in those who received chemotherapy alone, with R0 resection rates of 22.3 and 5.8 percent, respectively (Tang et al. 2020). The increased risk of relevant toxicities and need for a period of approximately six weeks off bevacizumab therapy prior to surgery must be taken into consideration when considering bevacizumab in this setting.

Initial studies of cetuximab plus FOLFOX and FOLFIRI indicated a small improvement in surgical resectability in cetuximab-treated patients (Bokemeyer et al. 2009; Van Cutsem et al. 2009). However, the subsequent New EPOC trial evaluating FOLFOX with or without cetuximab for patients with resectable liver-only metastases demonstrated an inferior progression free survival (22.2 v 15.5 months) and overall survival (81.0 v 55.4 months) for patients who received combination treatment with cetuximab, and is not recommended in this setting (Bridgewater et al. 2020).

Hepatic Arterial Infusion (HAI)

Liver metastases are perfused almost exclusively by the hepatic artery, while the normal liver hepatocytes derive their blood supply mostly from the portal vein (Breedis and Young 1954).

Table 7 Drugs for hepatic arterial infusion (HAI).

Drug	Half-life (min)	Estimated increased exposure via HAI
Fluorouracil (5-FU)	10	5–10-fold
5-fluoro-2-deoxyuridine (FUDR)	<10	100–400-fold
Bischlorethylnitrosourea (BCNU)	<5	6–7-fold
Mitomycin C	<10	6–8-fold
Cisplatin	20–30	4–7-fold
Adriamycin (doxorubicin hydrochloride)	60	2-fold

Table 8 Rationale for hepatic arterial infusion (HAI).

1. Liver metastases perfused by hepatic artery; normal liver by portal vein.
2. Some drugs extracted by liver during first pass; less systemic toxicity.
3. Liver may be only site of metastatic disease; stepwise pattern of metastatic progression.

Additionally, certain drugs are largely extracted by the liver during the first pass through the arterial circulation, which results in high local concentrations of the drug with minimal systemic toxicity. In 1978, Ensminger and colleagues demonstrated that 94–99% of floxuridine (FUDR) is extracted by the liver during the first pass, compared to 19–55% of 5-FU. Drugs with a high total body clearance and short plasma half-life are more useful for hepatic infusion (Table 7) (Ensminger et al. 1978). The liver is often the first and only site of metastatic disease and it is possible that hematogenous spread occurs via the portal vein to the liver, and then from the liver to other organs. Therefore, aggressive treatment of metastases confined to the liver may prolong survival. Rational for hepatic artery infusion therapy is described in Table 8.

Regional hepatic arterial therapy can be delivered using either an intra-arterial catheter connected to an external pump or a fully implanted pump. Early studies with percutaneously placed hepatic artery catheters produced high response rates, but clotting of the catheters or the hepatic artery, duodenal ulcers, and bleeding from around the catheters (Tandon et al. 1973) led physicians to abandon this method. The development of a fully implanted pump allowed long-term hepatic artery infusion (HAI) with a lower incidence of complications (Ensminger et al. 1981).

Toxicity of Hepatic Arterial Infusion

The most common adverse effects of HAI FUDR therapy are gastrointestinal ulceration and biliary sclerosis. The bile ducts derive their blood supply almost exclusively from the hepatic artery (Northover and Terblanche 1979), and thus are also perfused with high doses of chemotherapy through HAI. Myelosuppression, nausea, vomiting, and diarrhea do not occur with HAI therapy using FUDR. If diarrhea does occur, shunting to the bowel should be suspected (Gluck et al. 1985).

Clinically, biliary toxicity is manifested as elevations of aspartate transaminase, alkaline phosphatase, and bilirubin. In the early stages, hepatic enzyme elevations will return to normal when the drug is withdrawn and the patient is given a rest period, though can become permanent. Therefore, careful monitoring of liver function tests is necessary to avoid this toxicity.

In patients who develop jaundice, an endoscopic retrograde cholangiopancreatogram (ERCP) may demonstrate lesions resembling idiopathic sclerosing cholangitis. The strictures may be focal and present at the hepatic duct bifurcation, and therefore drainage procedures may be helpful.

Hepatic Arterial Infusion for Unresectable Metastatic Colorectal Cancer

In the Cancer and Leukemia Group B (CALGB) trial, metastatic colorectal cancer patients were randomized to either HAI FUDR, LV, and dexamethasone, or to intravenous 5-FU plus LV. The primary endpoint was survival, and a statistically significant survival advantage was seen with HAI relative to systemic 5-FU/LV (24 vs. 20 months, p = 0.0034). The response rate was also higher in the HAI arm at 48% versus 25% (p = 0.001), as was the hepatic disease-free survival (9.8 vs. 7.3 months, p = 0.034) (Kemeny et al. 2006). Other endpoints concerned correlation of survival with tumor biology, assessment of clinical response and toxicity, and economic analysis (Kemeny et al. 2003). Quality of life using the Rand 36-Item Health Status Profile, Memorial Symptom Assessment Scale, and other instruments demonstrated an improvement in physical functioning in the HAI group (Kemeny et al. 2006).

Additional trials evaluating more modern chemotherapy regimens including oxaliplatin and irinotecan followed. In a phase I study of HAI FUDR and systemic irinotecan in 46 pretreated patients, the combination was found to be safe and tolerable at the maximum tolerated dose, with a response rate of 74% observed, and median overall survival of 20 months (Kemeny et al. 2001). A subsequent phase I trial identified the combination of HAI FUDR and systemic m-FOLFOX6 as safe and tolerable, with overall response rate of 68.6% for hepatic metastases and overall survival of 25 months in 35 patients (Li et al. 2014). Additional phase I studies evaluating various combinations of systemic and hepatic arterial infusion regimens have generally identified this overall strategy as safe and tolerable. The combination of HAI FUDR and systemic chemotherapy with cetuximab was evaluated in a multicenter phase II trial which was significant for median OS of 35.2 months and no toxicity concerns (Levi et al., 2016). However, the addition of systemic bevacizumab to chemotherapy with oxaliplatin- or irinotecan-based regimens was associated with greater biliary toxicity in a phase II trial (Kemeny et al. 2011).

There are currently no randomized data comparing systemic chemotherapy ± HAI FUDR, though clinical trials evaluating such are currently ongoing. Retrospective data comparing systemic chemotherapy with or without HAI FUDR in patients with hepatic metastatic colorectal cancer demonstrated an overall survival of 32.8 vs 15.3 months (p<0.001) (Dhir et al. 2017), though low rates of conversion to resection and shorter than expected survival in the chemotherapy alone cohort limit interpretation of these results (Karanicolas and Ko 2017).

Conversion to resectability has been evaluated in colorectal cancer patients with unresectable hepatic metastases treated with HAI FUDR and systemic chemotherapy. In a phase I trial of HAI FUDR and systemic oxaliplatin and irinotecan in patients with extensive hepatic metastatic disease, 47% of all patients and 57% of treatment-naïve patients underwent complete resection (Kemeny et al. 2009). In a phase II trial of 49 patients with unresectable colorectal cancer liver metastases, an overall response rate of 76% was seen, with 47% achieving conversion to resection at six months (D'Angelica et al. 2015). These results are favorable when compared to historically reported outcomes with chemotherapy alone, but no randomized data exist.

Adjuvant HAI

Once metastases grow beyond 3 mm, they obtain their blood supply from arterial circulation, while the normal hepatocytes continue to receive blood flow from the portal vein (Archer and Gray 1989). With hepatic resection of liver metastases, residual disease, if present, may be 2–3 mm in diameter, and therefore derive its blood supply from the hepatic artery.

Based on this rationale, randomized trials have been performed to address the question of the utility of adjuvant therapy with HAI after liver resection. At Memorial Sloan-Kettering Cancer Center (Kemeny et al. 1999), patients were randomized after liver resection to HAI FUDR plus dexamethasone and systemic 5-FU +/−LV, or systemic chemotherapy alone. The primary endpoint of survival at two years was significantly increased with HAI plus systemic chemotherapy (86% vs. 72%, p = 0.03). An update with a median follow-up time of 10 years revealed a 10-year survival of 40% for the HAI + systemic therapy group and 27% for the systemic therapy-alone group. The two-year time to hepatic recurrence was also increased in patients treated with HAI plus systemic therapy and was 90% and 60%, respectively (Kemeny and Gonen 2005). Median time to hepatic recurrence had not been reached in the HAI + systemic therapy arm, but was 32.5 months in patients treated with systemic therapy (p = 0.01). The overall progression-free survival was 31.3 months versus 17.2 months (p = 0.02) (Kemeny and Gonen 2005).

The Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG) conducted a prospective trial of hepatic resection alone versus resection followed by HAI (FUDR) and systemic infusional 5-FU (Kemeny et al. 2002). Only patients with three or less hepatic metastases were enrolled, and because patients were randomized prior to resection, 29 patients were found to be ineligible at the time of surgery. For the 75 patients who entered the study, the primary endpoint of four-year disease-free survival was significantly longer with HAI plus systemic therapy versus resection alone, 58% and 34%, respectively ($p = 0.039$). The study was not powered for overall survival, but the five-year survival rate was 58% for the HAI and systemic group and 40% for the resection-only group (Kemeny et al. 2002).

The combination of FUDR with systemic capecitabine and oxaliplatin chemotherapy has also been evaluated in a phase II study of 55 patients. In this trial, patients received alternating courses of HAI FUDR and dexamethasone weeks 1 and 2, and systemic therapy with capecitabine and oxaliplatin weeks 4 and 5. The primary endpoint of the trial was met with a two-year overall survival of 88% (Alberts et al. 2010). A randomized phase III trial to further evaluate this regimen, NASBP C-09, was unfortunately terminated early due to low accrual.

Data from a prospectively maintained database of patients with liver-limited metastatic colorectal cancer who underwent resection and treatment with systemic chemotherapy with or without HAI FUDR at Memorial Sloan Kettering has been evaluated for survival comparisons. In this population, HAI was administered in the pre- and/or post-operative setting, and all patients received pre- and/or post-operative systemic chemotherapy. Of 2368 total patients, 1442 received modern systemic chemotherapy regimens. The 10-year overall survival in this group was 67 months for those who received and 47 months for those who did not receive HAI. The hazard ratio adjusted by propensity score was 0.67 ($P<0.001$) (Groot Koerkamp et al. 2017).

Key Take Home Messages

- In patients with metastatic colorectal cancer, trials with triplet combination therapy using 5-FU, oxaliplatin and irinotecan show improved progression free and overall survival compared to two-drug regimens with 5-FU and oxaliplatin or irinotecan, at the expense of increased rates of high-grade toxicity.
- Addition of biologic agents should be made based on site of primary tumor; overall survival increased with addition of cetuximab vs bevacizumab for RAS wild type left-sided primary tumors, whereas the reverse was found for right-sided primary tumors.
- FOLFOX with or without cetuximab for patients with resectable liver-only metastases demonstrated an inferior progression free survival for patients who received combination treatment with cetuximab; therefore, cetuximab is not recommended in this setting.
- In the small subset of patients with metastatic colorectal cancer who have deficient mismatch repair or high microsatellite instability tumors, the first-line treatment of choice is immune checkpoint inhibitor therapy rather than cytotoxic chemotherapy regimens.
- Hepatic artery infusion with systemic chemotherapy can be used in patients with liver limited colorectal metastases who are unresectable and in the adjuvant setting.

Areas for Further Research

- The underlying mechanisms explaining differences in regimen responsiveness of right versus left sided colorectal cancer metastases is being further explored.
- There are currently no randomized data comparing systemic modern chemotherapy with or without hepatic artery infusion therapy for patients with liver limited unresectable colorectal metastases in patients. Trial enrollment sizes are small for evaluation of adjuvant hepatic artery infusion therapy.

Trusted Links for Further Reading

- Venook AP ND, Innocenti F, et al. Impact of primary tumor location on overall survival and progression-free survival in patients with metastatic colorectal cancer: Analysis of CALGB/SWOG 80405. Journal of Clinical Oncology. 2016;3504(34S).
- Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med*. Dec 3 2020;383(23):2207–2218. doi:10.1056/NEJMoa2017699.
- Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. Mar 2020;21(3):398–411. doi:10.1016/S1470-2045(19)30798–3.
- Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999 Dec 30;341(27):2039–48. doi: 10.1056/NEJM199912303412702. PMID: 10615075.

Interventional Radiology

Lisa Liu & Jonathan Lindquist

Locoregional Therapies to Induce Future Liver Remnant Hypertrophy and Improve Perioperative Outcomes

Complete surgical resection remains the first-line treatment for metastatic cancer to the liver, and is potentially curative with long-term survival benefit. However, up to 70–80% of patients are not candidates for surgical resection. One major potential barrier to surgical resection eligibility is inadequate future liver remnant (FLR) volume, which greatly increases the risks of postoperative liver failure and liver failure related mortality.

One of the strongest predictors of a patient's risk for poor perioperative outcomes is a small FLR percentage in relation to total functional liver volume (Kubota et al. 1997). Therefore, patients with a tumor burden requiring a large volume resection are at increased risk for liver failure. As discussed above under Surgical Therapy, for patients with normal liver function, a minimum of ≥20% FLR is the recommended threshold for safe resection, with some institutions preferring a cutoff of ≥20–30% (Dixon et al. 2021; Kishi et al. 2009; Vauthey and Mizuno 2017). Patients with chemotherapy-associated liver injury (CALI) or Child-Pugh A cirrhosis are at greater risk for postoperative liver failure in comparison to patients with normal liver function (Dixon et al. 2021). Therefore, for patients with steatosis and/or exposure to hepatotoxic chemotherapy, a minimum of ≥30% FLR is recommended for safe resection (Shindoh et al. 2013b; Vauthey and Mizuno 2017; Zorzi et al. 2007). For Child Pugh A cirrhotic patients with limited functional hepatic reserve, the recommended threshold increases to ≥40% (Azoulay et al. 2000; Clavien et al. 2007; Kubota et al. 1997; Vauthey and Mizuno 2017). For patients that do not meet these recommendations, locoregional and surgical therapies can be used to induce FLR hypertrophy to decrease their perioperative risks and thus bridge to surgical resection. In practice, FLR is calculated using volumetric software to analyze cross-sectional imaging such as CT or MRI. Mathematical calculations have been developed in an attempt to standardize FLR for body surface area and body (Ribero et al. 2008; Vauthey et al. 2002). Rate of growth following portal vein embolization (PVE) and degree of hypertrophy after PVE have also been shown to have prognostic value (Ribero et al. 2007a; Shindoh et al. 2013a).

Portal Vein Embolization

In the mid-1980s, Makuuchi was the first to describe using preoperative portal vein embolization (PVE) to atrophy the portion of the liver planned for resection and induce compensatory hypertrophy of the planned remnant liver (Madoff et al. 2005). PVE can also function as a "stress test" by providing a preoperative demonstration of the remnant liver's capacity for regeneration, which may be impaired in the setting of liver injury or poor liver functional reserve. Over a period of 2–8 weeks, PVE is expected to increase FLR volumes by approximately 40%, though individual patient characteristics can cause great variability in outcomes.

The oldest method of PVE involved an open surgical approach with direct puncture of the ileocolic vein; this has largely been supplanted by the minimally invasive image-guided percutaneous transhepatic approach. There are two main ways to access percutaneously: through the ipsilateral lobe that is targeted for resection versus the contralateral lobe that is the future liver remnant. The ipsilateral approach minimizes risk of causing iatrogenic damage to the future liver remnant but requires thoughtful planning to avoid accessing through tumor and risking tumor seeding. Additionally, the ipsilateral approach requires the interventional radiologist to intravascularly navigate more acute angles in order to appropriately position the catheter at the embolization target. Accessing contralateral is technically easier to navigate the catheter to the target but may increase the risk of injuring the future liver remnant from access attempts. A variety of embolic materials can be used to occlude the portal veins, such as coils, plugs, and particles. N-butyl cyanoacrylate glue has shown to have the best effect on FLR hypertrophy in recent studies (Ali et al. 2021; Luz et al. 2021).

General risks of PVE regardless of ipsilateral or contralateral approach include bleeding such as subcapsular hematoma and/or hemoperitoneum, infection such as cholangitis and/or hepatic abscess, bile duct damage and potential leak, damage to liver function, non-target embolization or migration of embolic coils or plugs, non-target portal vein thrombosis, and inadequate hypertrophy. Overall the risk profile for PVE is low. The Society of Interventional Radiology published quality improvement guidelines in 2010 recommending staying below a threshold of 11% morbidity and 6% major complications for PVE. A 2008 meta-analysis of 1088 patients who underwent PVE demonstrated only a 2.2% morbidity and 0% procedure-related mortality, keeping well within those parameters (Abulkhir et al. 2008).

As discussed above under Surgical Therapy, for patients with bilobar metastatic disease, a two-stage hepatectomy (TSH) approach may be an option to try to downstage to a potentially curative resection. In the first stage, tumor within the FLR is treated typically with surgical resection or thermal ablation. Once the FLR is free of viable tumor, the next goal is for PVE to increase the FLR volume before the second stage resection, especially since most of these patients also undergo neoadjuvant hepatotoxic chemotherapy, thereby increasing their perioperative risks.

While the majority of patients who undergo preoperative PVE successfully continue on to surgical resection, up to 30–40% of patients are not able to bridge to resection due to progression of liver tumor burden while waiting for hypertrophy (Sandström et al. 2018a). Not only is a lack of tumor control a concern during this waiting period, PVE may contribute to progression of disease (Hoekstra et al. 2013). Embolizing the portal inflow can instigate a compensatory increase in ipsilateral hepatic arterial inflow, also known as the hepatic artery buffer response. Studies have suggested in patients with colorectal metastases that PVE is associated with increased tumor growth rate, mitotic rate, and proliferation index Ki67 (de Graaf et al. 2009; Hoekstra et al. 2012; Simoneau et al. 2015). Recently hepatic vein embolization has been described in combination with portal vein embolization. This may improve degree of FLR hypertrophy and improve kinetic growth rate (Guiu et al. 2016; Hwang et al. 2015; Le Roy et al. 2017; Niekamp et al. 2020). Further study of this technique is ongoing.

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) was originally designed to induce rapid FLR growth rate, thereby decreasing the time interval to complete surgical resection. Compared to PVE or portal vein ligation (PVL) alone, the combination of liver partitioning and PVL achieves greater hypertrophy percentages of segments 2 and 3 in a shorter amount of time – only 1–2 weeks (Sandström et al. 2018a). However, given the controversial safety profile and lack of evidence for long term survival benefits as discussed above in more detail under Surgical Therapy, ALPPS currently is not commonly practiced.

Radiation Lobectomy

Transarterial radioembolization of the tumor-bearing lobe with radioactive microspheres has been described as a method of inducing FLR hypertrophy and provides concomitant tumor control (Malhotra et al. 2019; Gaba et al. 2009; Gabr et al. 2019; Teo and Goh 2015). Radioembolization, also known as selective internal radiation therapy (SIRT) is a catheter-directed infusion of radioactive microspheres.^{90}Yttrium-90 (Y90) is the most commonly used isotope, though other isotopes such as ^{166}Holmium (Ho166) can be used. Y90 is a pure beta-emitter with maximal tissue penetration range of 1 cm, allowing for local high intensity radiation. Historically, SIRT has been used as a salvage therapy for unresectable advanced colorectal liver metastatic disease (Jakobs et al. 2008). As an adjunctive therapy to first-line systemic chemotherapy, SIRT has been demonstrated to be a useful tool for tumor control in patients with colorectal liver metastases (Lewandowski et al. 2014). The neoadjuvant potential for SIRT was first described in 2008 when Jakobs et al. reported a case series of patients with colorectal liver metastases who had unilobar radioembolization. These patients had expected ipsilateral lobe atrophy, but also had contralateral lobar hypertrophy of 21% 30 days post-SIRT (Jakobs et al. 2008). Gaba et al. also described this phenomenon in patients with primary liver cancer and named the technique "radiation lobectomy" (Gaba et al. 2009). In contrast to palliative lobar radioembolization, radiation lobectomy is performed with the ultimate goal of curative surgical resection. Higher radiation doses are generally given to improve FLR hypertrophy (Entezari et al. 2021).

Radiation lobectomy provides the benefit of synchronous tumor control, but with the drawback that the rate of hypertrophy is slower than PVE (Gaba et al. 2009; Jakobs et al. 2008; Vouche et al. 2013). Radiation lobectomy related volumetric changes progress at a linear time-dependent rate, with continuous gradual hypertrophy until maximum FLR volumes are reached at nine months post procedure (Vouche et al. 2013). Patients with colorectal liver metastases are thought to have a similar pattern of hypertrophy after radiation lobectomy to those with primary liver cancer (Vouche et al. 2013). A 2012 animal study using swine models offered further insight by prospectively comparing hypertrophy after PVE and Y-90 lobectomy at three- and six-month follow-up intervals. PVE was associated with more rapid hypertrophy over one month that then plateaued, while Y90 lobectomy demonstrated a gradual yet persistent rate of hypertrophy with the volume gain of both groups converging at the 3–6 month follow-ups. Degree of hypertrophy has been shown to be closely related to absorbed radiation dose in the treated lobe (Liebl et al. 2021). Care must be taken not to overestimate the relatability of animal study results to predictions of human outcomes, even though these findings certainly corroborate Vouche et al.'s findings in their human patient population. In 2021, Bekki et al. published a retrospective comparison between radiation lobectomy and PVE in human patients with HCC, hypertrophy was followed out to six months with imaging and demonstrated greater hypertrophy with Y90 lobectomy of 63% compared to 26% in the PVE group. The PVE group did have a higher resectability rate of 85% compared to 64% in the Y90 group, with tumor progression as the most common reason to not pursue surgery, however the Y90 group also had 18% of patients not pursue surgery due to complete tumor control. Complete response per RECIST criteria was achieved in 50% of the Y90 lobectomy group (Bekki et al. 2021).

While the interest in radiation lobectomy has grown since first described, data remains limited with few comparative investigations. Additionally, most studies focus on primary liver cancer patients, primarily HCC. Patients with secondary liver cancer are likely to respond differently for a multitude of reasons including differences in comorbid liver conditions (less likely to be cirrhotic, though more likely to be exposed to hepatotoxic chemotherapies), differences in tumor pathophysiology, and differences in treatment pathways. Garlipp et al. performed a retrospective comparison using matched pair analyses PVE and Y90 lobectomy in patients with colorectal metastatic liver disease, however hypertrophy outcomes were compared at a short one month follow-up which led as expected to PVE being associated with greater hypertrophy compared to Y90 lobectomy (Garlipp et al. 2014). In 2020, Kurilova et al. described two patients with colorectal liver metastases who both failed PVE with insufficient FLR increase. The first patient underwent Y90 multisegmentectomy for a target radiation dose of 120 Gy 5 months after PVE and experienced a 13% FLR increase and partial tumor response, which allowed for the patient to proceed to right extended hepatectomy (Kurilova et al. 2020). This patient developed a solitary lung metastasis one-year post-resection and passed away 32 months post-Y90 without evidence of recurrent hepatic disease. The second patient underwent right lobar Y90 with a targeted dose of 120 Gy two months after PVE and experienced a 59% FLR increase over 7 weeks of follow-up with partial tumor response, allowing the patient to proceed to extended right hepatectomy and intraoperative radiofrequency ablation of a segment III lesion. There was no evidence of recurrence at 26 months follow-up (Kurilova et al. 2020).

Other Trans-arterial Therapies

The risk of inadequate FLR hypertrophy after PVE is much lower than the risk of disease progression, estimated to be less than 5%. Patient history of CALI, cirrhosis, and/or diabetes can increase the risk of inadequate hypertrophy. For these patients, adjunct or simultaneous locoregional therapies can be used to further stimulate hypertrophy. As described above, radiation lobectomy has been used successfully as a salvage therapy to bridge to surgical resection in patients with colorectal metastases to liver who failed PVE (Kurilova et al. 2020).

Bland trans-arterial embolization (TAE) does not involve any brachytherapy but instead relies on a macrovascular embolic effect, resulting in ischemic inflammation and necrosis of the target liver parenchyma/tumor which then stimulates compensatory hypertrophy of the non-targeted liver parenchyma. While TAE alone can induce hypertrophy, it is to a lesser degree than PVE alone; therefore, TAE is typically utilized as a salvage therapy after failed PVE. Case reports of TAE to colorectal liver metastases after PVE failure have been described with successful cumulative augmentation of FLR volume and subsequent bridging to surgical resection (Gruttadauria et al. 2006).

Locoregional Therapies for Treatment of Hepatic Metastatic Disease

Ablative Therapies

Broadly speaking, "ablation" in the medical field is simply defined as the removal or destruction of tissue. In relation to therapy of liver tumors, ablation refers to a category of image-guided minimally invasive techniques using temperature, non-thermal electrical applications, or intratumoral injection of chemicals to cause local destruction of tumor. Ablation can use ultrasound, CT, MRI, or PET/CT imaging guidance and has been performed percutaneously as well as intraoperatively. Most ablation therapies utilized in treatment of liver metastases fall under the category of thermal ablation, involving the application of extreme temperatures to destroy tumors. Radiofrequency Ablation (RFA) and Microwave Ablation (MWA) are techniques that both utilize extreme heat to char the tumor and are the most common ablative technique used in the United States for liver metastases. Laser Interstitial Thermotherapy (LITT) and High-Intensity Focused Ultrasound (HIFU) are also therapies based on heat production; the former uses infrared optical fiber transmission of infrared light to produce heat, while the latter is a noninvasive technique that focuses ultrasound waves at a targeted distance to create vibrations and produce heat (Cheung et al. 2021; Filippiadis et al. 2021). Meanwhile, cryoablation utilizes alternating cycles of freezing and thawing to cause cell apoptosis (Lin et al. 2021). A recently developed non-thermal technique called Irreversible Electroporation (IRE) applies an electrical field to induce cell death (Narayanan 2015). Chemical ablation, the percutaneous intratumoral injection of ethanol or acetic acid, has been used as a treatment for patients with HCC, but has not been found to be as effective in treatment of metastatic liver disease due to differences in the pattern of intratumoral distribution between HCC tumors and liver metastases (Bartolozzi and Lencioni 1996; Mastrolonardo et al. 2020; Swierz et al. 2020). Here we will focus on RFA, MWA, cryoablation, and IRE.

Treatment Algorithm and Patient Selection

As a parenchyma-sparing and minimally invasive therapy, ablation has the flexibility to fulfill multiple roles in the treatment of metastatic liver disease. Approximately 70–80% of patients are not candidates for surgical resection due to comorbidities, tumor burden, tumor proximity to key vascular or biliary structures, or inadequate future liver remnant. For unresectable colorectal liver metastases, ablation has been used solo or in combination with other systemic, locoregional, or surgical treatments for goals of palliative tumor burden control, bridging, or downstaging to curative surgical resection. For patients who do undergo surgical resection, many patients experience local recurrence of liver metastases. Therefore, ablation has also demonstrated utility as a salvage therapy for patients with postoperative recurrence (Lin et al. 2021). Due to its low risk profile, ablation is typically able to be safely repeated multiple times as needed, and/or can be planned as a course of multiple staged procedures (Nielsen et al. 2013).

Traditionally surgical resection has been considered the only curative treatment for metastatic liver disease, however, as ablation techniques and understanding of patient selection improve so do the outcomes – recent ablation studies document up to 50% five-year survival rates, which is comparable to surgical resection outcomes (Filippiadis et al. 2021). Specifically for a subgroup of patients with small (≤3cm) tumors, multiple retrospective comparison studies have suggested that RFA and MWA are comparable to surgical resection as a potentially curative therapy (Lin et al. 2021). Although curative potential has been documented in tumors 3–5 cm, the greater the size of the tumor the greater the risk of inadequate ablative margins and subsequent local tumor progression increases; therefore, curative intent for ablation is not recommended for tumors >5 cm (Gillams et al. 2015). An ablative margin of >5 mm is preferred and >10 mm is considered ideal (Shady et al. 2018). An international phase III single-blind randomized clinical trial, Colorectal Liver Metastases: Surgery vs Thermal Ablation (COLLISION), is currently underway and pending results at the time of this publication comparing the long-term outcomes of thermal ablation versus surgical resection for this subgroup of patients with tumors ≤3cm (Puijk et al. 2018).

In addition to individual tumor size, the number of liver metastases and total tumor volume also impact the risk of incomplete ablation and post-ablation local tumor progression. Though solitary tumors are associated with the best outcomes, as many as nine tumors in a single patient have been documented as treated by thermal ablation. In a consensus statement by the International Oncology without Frontiers meeting in 2013, five or less tumors were recommended to be routinely considered for ablation, while nine or less could be considered for ablation depending on the individual situation (Gillams et al. 2015).

Colorectal molecular tumor markers may have prognostic value following ablative therapies. Thermal ablation of KRAS-wild type tumors with margins greater than 1 cm demonstrate virtually no residual tumor, but high Ki-67 ratios and RAS mutant tumors may be more ablation resistant and require greater margins and/or repeat ablation procedures (Calandri et al. 2018; Filippiadis et al. 2021). Understanding how different tumor markers may correlate to treatment response is important for appropriate counseling of patient expectations.

In general, the risk profile for ablation regardless of method is favorable – per the 2020 statement by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) "Standards of Practice for Thermal Ablation of Liver Tumors," major complications graded 2–6 per the CIRSE grading system occur less than 5% (Crocetti et al. 2020). However, challenging patient selection or improper technique may increase risks on an individual basis. If the planned ablation zone includes or runs close to the main bile duct, then thermal ablation may cause bile duct stenosis or leak, with possible subsequent cholangitis or abscess. An ablation zone too close to major hepatic venous or portal venous structures may cause venous thrombosis and liver infarction. Patients with normal coagulopathy have a low risk of bleeding. Puncture-related complications (bowel perforation, pneumothorax/pleural effusion) are also low risk with appropriate image guidance techniques (Lahat et al. 2014). Tumor seeding along the percutaneous tract is a serious though rare risk, occurring in <1% of patients with colorectal liver metastases in a retrospective study of 1462 patients and 2530 tumors treated by MWA (Yu et al. 2012). Though not well studied in the metastatic liver disease population, in patients with HCC the proper technique of ablating the tract during electrode/antenna removal at the end of the procedure has been shown to markedly reduce risk of tumor seeding from as high as 12% down to 0–1% (Francica 2017). Avoiding a subcapsular approach is also important to minimize risk of tract seeding. The CIRSE 2020 Standards of Practice therefore recommend the following contraindications for thermal ablation: (1) tumor within 1 cm distance from the main bile duct, (2) significant ascites along the planned percutaneous approach, (3) exophytic tumor without option for trans hepatic approach, and (4) uncorrectable coagulopathy defined as INR <1.5 or platelet count <50,000 (Crocetti et al. 2020).

Radiofrequency Ablation (RFA)

RFA has been used in medical applications since the early 1990s for a multitude of pathologies from aberrant cardiac conduction pathways to various primary and metastatic cancers, including in the liver. In RFA of primary or secondary liver tumors, a probe(s) with an electrode at the tip is placed percutaneously or intraoperatively into the target lesion. The electrode generates a high-frequency alternating electrical current in the radiofrequency range (approximately 375–500 kHz), which induces rapid ionic oscillation and subsequent frictional heating in the nearby tissues (Hong and Georgiades 2010). The core ablation zone aims to reach temperatures between 60–100°C which induce protein denaturation and coagulative necrosis. Temperatures of 50–60° C within a marginal transitional ablation zone cause cytotoxic damage though not necessarily complete necrosis – therefore non-target tissues and structures within this zone can potentially be damaged, while tumor within this zone may be inadequately treated. On the other end of the spectrum, if the core ablation zone temperatures reach 100°C or greater, water evaporates and the tissue desiccates, which leads to impedance of the electrical current and also results in suboptimal treatment (Filippiadis et al. 2021).

In RFA, the volume of surrounding tissue that is exposed to direct heating is relatively small, and the creation of the majority of the ablation zone depends on the principle of thermal conductance. Because of this reliance on conductance, the presence of large vascular structures (≥3 mm in diameter) within close proximity to the desired ablation zone (within 1 cm) becomes important to note. The flow within these nearby blood vessels causes a local cooling effect, affecting the conductance of heat. This phenomenon, known as the heat sink effect, can help protect the blood vessels themselves from adverse effects. However, it can also decrease the effective ablation zone and thus lead to inadequate ablation margins (Kim 2018).

Since RFA is an older technique than MWA, relatively it has a larger published body of data on outcomes with longer follow-up periods demonstrating its benefits for long-term survival in patients with both unresectable and resectable colorectal liver metastases (Izzo et al. 2019). A phase II randomized clinical trial compared long term survival of patients with unresectable colorectal liver metastases treated with standard of care systemic oxaliplatin-based chemotherapy alone vs. chemotherapy plus RFA and/or resection and found significant long term overall survival benefit associated with combination therapy: 43% vs. 30% five-year survival and 36% vs. 9% eight-year survival. Of note, 52% of patients in the combination treatment arm underwent systemic chemotherapy plus RFA only, 46% underwent chemotherapy with both RFA and resection, and only one patient underwent chemotherapy with resection only (Ruers et al. 2017).

For patients with advanced bilobar disease or otherwise large tumor burden, RFA can be utilized to provide aggressive local tumor control while sparing future liver remnant parenchyma, in order to downstage their disease and allow for surgical resection. RFA has been used in combination with single stage or two stage hepatectomy allowing for successful progression to surgical resection (Imai et al. 2017; Okuno et al. 2021). For patients who experience recurrence after hepatectomy or after previous thermal ablation, RFA provides a minimally invasive salvage therapy that can obtain local tumor control and can be repeated multiple times as needed (Dupré et al. 2017; Fan et al. 2020; Nielsen et al. 2013; Sofocleous et al. 2011; Zimmermann et al. 2020).

As experience with RFA has grown, understanding of optimal patient selection has also grown. Multiple retrospective studies have suggested that RFA has curative potential comparable to that of surgical resection for tumors ≤3cm (Kim et al. 2011; Luo et al. 2020; Mulier et al. 2008). Since RFA is associated with a lower risk profile compared to surgical resection, some institutions may favor a "test of time" approach in which thermal ablation is utilized first to allow for the chance of local cure without the morbidity and mortality risks of surgery; provided the patient undergoes close imaging follow-up, thermal ablation does not exclude the possibility of performing surgical resection later if ablation is not successful (Filippiadis et al. 2021).

Microwave Ablation (MWA)

The first microwave ablation generators were approved by the FDA in the early 2000s. Like RFA, MWA uses heat to cause protein denaturation and coagulative necrosis of tumor cells. However, MWA involves higher frequencies in the range of 915 MHz or 2.45 GHz. Instead of applying direct heat to a small surrounding volume and using thermal conductance to create the majority of the ablation zone as RFA does, MWA induces dielectric hysteresis which applies direct heat to a larger surrounding area, with only a minority of the therapeutic ablation zone depending on thermal conductance. In other words, MWA achieves higher temperatures (up to 150°C), over a larger zone, and at a faster rate compared to RFA. Since the majority of the MWA ablation zone depends on rapid direct heating instead of thermal conductance, the issues of (1) electrical impedance at temperatures greater than 100°C and (2) the heat sink effect from nearby large vessels do not impact the efficacy of MWA as much as they do in RFA (Kim 2018). Another technical benefit of MWA is that a significantly smaller marginal transitional ablation zone has been demonstrated with MWA compared to RFA, cryoablation, and IRE in an *in vivo* animal study using swine models (Cornelis et al. 2017).

MWA's inherent decreased susceptibility to the heat sink effect is considered to give it an advantage over RFA for treatment of tumors that are within 1 cm of blood vessels ≥3 cm in size. A retrospective comparison study demonstrated comparable local progression free survival and long term overall survival outcomes between RFA and MWA, however perivascular tumors were associated with an increased risk of post-ablation local tumor progression in the RFA group, but not with the MWA group (Shady et al. 2018).

Although MWA should be considered over RFA for treatment perivascular tumors, for patients with peribiliary tumors MWA may be associated with greater risks of bile duct damage due to the increased heat (Lin et al. 2021). Overall, the risk profile still remains low; comparative systemic reviews of RFA and MWA demonstrate an overall risk of major complications <5% and procedure-related mortality <1% for both RFA and MWA (Bertot et al. 2011; Lahat et al. 2014).

Although no prospective randomized trials comparing RFA and MWA treatment of liver metastases currently exist, retrospective data has largely demonstrated the two to be at least equivalent in safety and efficacy. A few retrospective studies have suggested better progression-free survival associated with MWA compared to RFA, but these findings may have been confounded by RFA typically being performed during an earlier time period than MWA, associated with historical differences in patient selection (Izzo et al. 2019; Lin et al. 2021).

Given that MWA is considered comparable to RFA, comparisons between MWA and resection for liver metastases ≤3 cm have been of great interest. Multiple retrospective comparison studies have been published in recent years. One recent propensity matched retrospective comparison in Sweden evaluated 82 MWA patients and 645 resection patients with colorectal liver metastases ≤3 cm and found equivalent three year overall survival rates of 76% and 76% (Tinguely et al. 2020). Another recent propensity matched retrospective comparison study evaluated 189 ablation (RFA or MWA) patients and 152 resection patients with colorectal liver metastases ≤3 cm and found no significant difference in local tumor progression or overall survival, though there was a significant difference between ablation and resection groups with tumor(s) measuring 3–5 cm (Luo et al. 2020). Yet another retrospective comparison study from 2021 also demonstrated that while the five-year local tumor progression rate was higher with MWA compared to resection, there was no significant difference in five-year overall survival between MWA and surgical resection groups for colorectal liver metastases ≤3 cm – 45% vs. 46% MWA vs. resection respectively – while also finding a higher rate of major complications associated with surgical resection (Zhao et al. 2021). As the results of prospective randomized clinical trial data is still pending at the time of this publication, first-line practices for liver metastases ≤3 cm may be institution-dependent but should always involve a multidisciplinary discussion for each patient.

Cryoablation

In contrast to the extreme heat of RFA and MWA, cryoablation creates below freezing temperatures to induce tumor necrosis.

Traditionally cryotherapy used liquid nitrogen as a cooling agent, but modern cryoablation technology is argon-based and relies on the Joule-Thomson effect, in which the expansion of a real gas in a vacuum leads to a decrease in the temperature of the gas. Application of the Joule-Thomson effect to the argon gas within the cryoablation probe lumen rapidly cools the tip of the probe and forms an ice ball that freezes the surrounding tissues to a therapeutic range of -20°C to -40°C and causes direct cellular damage. Freezing is then alternated with a period of thawing, which causes even more cellular damage via swelling from osmosis of extracellular water to intracellular and recrystallization. Repeat-freeze-thaw cycles cause the cells to rupture and induce apoptosis. Similar to the heat-based ablation, cryoablation is also characterized by a marginal transitional zone where temperatures reach a range from 0°C to -20°C, which is low enough to cause cytotoxic damage but possibly not complete necrosis (Erinjeri and Clark 2010; Lin et al. 2021).

Cryoablation was one of the earliest thermal ablation methods used for metastatic liver disease, typically as a palliative/salvage therapy or to provide local tumor control in conjunction with systemic chemotherapy and/or surgical resection. Currently, it is one of the least common thermal ablation methods used in this population. Early retrospective single institution reports suggested some benefit for local tumor control but studies ranged widely in their reported efficacy, with local recurrence rates reported anywhere from 8% to 60% (Seifert and Junginger 2004). Though it is difficult to draw a definite conclusion from these studies due to the high heterogeneity of patient and tumor characteristics included in these data sets, during this time period RFA was also being simultaneously explored as a local treatment option and seemed to demonstrate generally lower local recurrence rates approximately 2–3% (Seifert and Junginger 2004). Similar to RFA, cryoablation is also susceptible to the heat sink effect in the setting of nearby large blood vessels, which may contribute to occurrences of local recurrence after cryoablation.

Furthermore, one study comparing intraoperative RFA and cryoablation for liver metastases demonstrated a much higher complication rate with cryoablation – 41% compared to 3% (Pearson et al. 1999). A particularly severe complication that is unique to cryoablation is cryoshock. Especially associated with large-volume cryoablations, the inflammatory reaction from cryoablation can exacerbate into a cytokine-mediated systemic inflammatory response that can present with hemodynamic instability, respiratory distress, disseminated intravascular coagulation (DIC), multi-organ failure, and death. In a 1999 international survey of operators with cryotherapy experience, a 1% rate of cryoshock in more than 2000 patients was reported, with 29% of those patients progressing to cryoshock-related death (Seifert and Morris 1999). Cryoablation has also been suggested to have a higher risk of bleeding compared to heat-based ablation, as it lacks the local cauterization effect that is inherent to RFA or MWA. The combination of fear of potentially devastating complications and supposed inferior efficacy to other ablative methods has led to a decline in the use of cryoablation for liver metastases after the 2000s.

Cryoablation demonstrates some unique features, however, that can potentially provide benefit over RFA for select patients. Unlike RFA or MWA, in cryoablation the ablation zone can be visualized intraprocedurally as the ice ball shows up well on ultrasound or cross-sectional imaging. Therefore, the ablation margins can be visualized in real time during the procedure and can be reacted to as needed. Cryoablation may also be associated with decreased pain compared to RFA or MWA (Littrup et al. 2016).

Multiple probe cryoablation techniques may also have greater efficacy compared to RFA for larger tumors. One comparative retrospective series found in a subgroup of patients with tumors >3 cm in diameter that cryoablation demonstrated a lower six month local recurrence rate of 17% compared to 38% with RFA (Bilchik 2000). Additionally, more recent retrospective data from suggests an improved efficacy and safety profile with modern advancements in cryotherapy techniques. One series investigating cryoablation in both primary and secondary liver cancer demonstrated a local tumor progression rate within the colorectal liver metastases group of 13% at one year and 22% at three years. The major complication rate was 6%, including three deaths due to cryoshock. However, these instances of cryoschock occurred early on in the series. Partway through the series, pre-procedure thresholds of platelets >100,000 and tumor size <4 cm were found to decrease major complication and cryoshock mortality rate decreased to 3% and 0%. Another change in protocol made halfway through the series involved switching from using preoperative aminocaproic acid to preoperative methylprednisolone, as the former was associated worse post-procedure anemia and thrombocytopenia, while the latter was associated decreased drops in hematocrit and platelets. Preoperative methylprednisolone was not given to diabetic patients (Littrup et al. 2016). Though comparative analyses of more recent cryoablation techniques with other modes of ablation are lacking, recent advances keep cryoablation in consideration as a unique and viable option for local control of liver metastases.

Irreversible Electroporation (IRE)

IRE is a novel non-thermal method of ablation that emits high voltage electrical pulses between two electrodes to create a destabilizing electrical field and cause irreversible nanopore defects in cell membranes to form (Narayanan 2015). Initially, reversible electroporation was explored in conjunction with cytotoxic drugs as a means of transiently increasing the cell membrane permeability to effectively delivering chemicals intracellularly, also known as electrochemotherapy. The theoretical concept of purposely pursuing irreversible electroporation for ablative intent was first proposed in 2005 (Davalos et al. 2005). Subsequent *in vitro* and *in vivo* animal studies demonstrated that while IRE is effective in causing cell apoptosis and death, structures composed of extracellular connective tissue matrix such as blood vessels, bile ducts, and nerves are not damaged within the ablation zone (Maor et al. 2007; Miller et al. 2005). An additional benefit is that the heat-sink effect does not apply to IRE (Narayanan 2015).

The implications for increased efficacy and safety in treating perivascular, periductal, or perineural lesions spurred interest in progressing applications of this technique to human subjects. In 2011 a preliminary safety investigation in the 38 human volunteers with 69 tumors in a variety of different organs was published. four out of the first eight patients experienced transient ventricular arrhythmias, a risk that was mitigated in the subsequent 30 patients with implementation of ECG-synchronized delivery (Thomson et al. 2011). A history of cardiac arrhythmias or being pacemaker dependent are therefore generally considered contraindications to IRE. Epilepsy has also been considered an exclusion criteria in some studies on a theoretical basis (Meijerink et al. 2021; Scheffer et al. 2014).

Currently there is one IRE device that is commercially available, the NanoKnife (Angiodynamics, Amsterdam, the Netherlands). The NanoKnife has a FDA 510 k clearance for soft tissue ablation; other uses are considered off-label. There are two types of IRE probes: monopolar and bipolar. The distance between the two poles needs to be precise for an optimal ablation zone. Two monopolar probes should be placed parallel at an ideal distance of approximately 1.5 to 2 cm apart for optimal ablation, which limits the size of the potential ablation zone. However, up to six monopolar IRE probes can be placed and simultaneously ablated to create a larger ablation zone. A bipolar IRE probe involves a single probe with two poles. General anesthesia with complete neuromuscular blockade is a requirement for IRE, as the high voltages involved would otherwise stimulate skeletal muscle contraction and cause movement of the probes during the procedure (Narayanan 2015).

A number of single arm prospective studies have already specifically investigated the utility of IRE in metastatic liver patients. A prospective registry was performed from 2009 to 2011 of 44 primary and secondary liver cancer patients undergoing 48 hepatic IRE procedures demonstrating a safe low risk profile, with 5 patients experiencing 9 mild adverse events which resolved within 30 days. None of the adverse events were a cardiac arrhythmia. The 3-month, 6-month, and 12-month local recurrence free survival rates for colorectal metastases were 100%, 94%, and 59%; for metastases from other primaries, local recurrence free survival was 100% at 12 months. No tumor size subgroup analysis for colorectal metastatic patients was performed, but local recurrence free survivals for all tumors <3 cm were 100% at 6 months and 98% at 12 months (Cannon et al. 2013).

COLDFIRE-1, a prospective safety and feasibility study investigating IRE in 10 patients with colorectal liver metastases, was designed as an ablate-and-resect study and also demonstrated a low-risk safety profile. Ten patients were included with resectable or otherwise locally treatable colorectal liver metastases, at least one of which had to be ≤3.5 cm – though one of the tumors was found to be >3.5 cm intraprocedure. There were 9/10 IRE procedures that were technically successful; one patient experienced an adverse event, a transient ventricular arrhythmia, which ceased and did not return once an electrode close to the diaphragm was removed, but was counted a technical failure as not all 90 pulses could be completed. Surgical pathology from resection of the treated lesions demonstrated complete tumor necrosis in 8/10 patients, with the one tumor that was >3.5 cm demonstrating near complete necrosis with a 1 mm margin of viable tumor, and one inconclusive due to damage to the specimen during resection (Scheffer et al. 2014).

COLDFIRE-1 was followed up by COLDFIRE-2, a single arm prospective study. The inclusion criteria greatly differed from COLDFIRE-1, recruiting 51 patients with ≥5.0 cm tumors that were not candidates for surgical resection or thermal ablation. Contrary to the previous studies, an overall complication rate of 40% was seen, including one death (2% mortality rate) within 90 days of the procedure after developing of biloma. A 1-year local recurrence free survival rate of 68% was seen, compatible with Cannon et al.'s previous local recurrence outcomes (Meijerink et al. 2021). However, given the greater risk profile seen in COLDFIRE-2 and the overall heterogeneity in inclusion criteria across the existing literature, additional research is warranted to further narrow the appropriate metastatic liver cancer patient selection for IRE.

Radioembolization

Radioembolization can be used for treatment of unresectable liver metastatic disease. The most studied metastatic cancer to the liver has been colorectal cancer, though radioembolization has been employed in numerous different cancers. Radioembolization is a brachytherapy that delivers radioactive microspheres to the tumor via the arterial bloodstream. Microspheres lodge at the end arteriole. Radioembolization takes advantage of the liver's dual blood supply. Non-cirrhotic liver parenchyma derives approximately 70–80% of blood from the portal vein with the remaining 20–30% supplied by the hepatic artery (Kan and Madoff 2008). Primary and metastatic liver tumors generally derive a greater proportion of their blood supply from neovascular hepatic arteries (Choi et al. 2014). The differential in blood supply between arterially supplied tumor and portal supplied liver parenchyma is used to improve delivery of locoregional therapies. As mentioned above under "Radiation Lobectomy," Yttrium-90 (Y90) is the most commonly used isotope for radioembolization. Y90 is a pure beta emitter, and has a half-life of 64.2 hours (Volchok and Kulp 1955). Various treatment strategies can be used depending on the goal of therapy, distribution of disease, and functional hepatic reserve. In patients with disease limited to one or two Couinaud segments, radiations segmentectomy can be employed. Very high radiation doses are given, and intent of treatment is curative (Lewandowski et al. 2018; Riaz et al. 2011). In patients with more extensive disease, lobar or bilobar delivery is performed. For those patients with bilobar disease, right and left lobar treatments are commonly separated by 5–8 weeks (Salem et al. 2019). Radiation lobectomy can also be used to induce FLR hypertrophy and has been discussed previously above (Malhotra et al. 2019).

There have been several studies specifically focused on radioembolization for patients with colorectal liver metastases. The randomized SIRFLOX and EPOCH trials used a bilobar radioembolization approach in metastatic colorectal cancer and demonstrated improved progression free survival in the liver in first line and second line settings (Mulcahy et al. 2021b; Van Hazel et al. 2016). These trials failed to demonstrate improved overall survival, which may be related to patients being included that had limited extrahepatic disease and primary tumors in place. Improved liver progression-free survival came at the cost of increased toxicity (Mulcahy et al. 2021b; Van Hazel et al. 2016). The RESIN registry observed 498 participants treated with Yttrium-90 resin microspheres; 17% were treated first-line, 41% second-line, and 43% third-line or beyond. Median overall survival was 15.0 months and median progression-free survival was 7.4 months. Grade 3 or 4 toxicities were seen in 8.4%, and were more common in third-line or greater therapies (Emmons et al. 2022). Future studies limited to patients with liver only metastatic disease and resected primary may show benefit. Additionally, targeted radioembolization of liver metastases may confer improved results when compared to the broad bilobar treatment strategy used in these trials. Further detailed information regarding this strategy for treatment of colorectal liver metastases is described below under "Radiation Therapy – Yttrium-90."

Radioembolization has also been studied for the treatment of breast, neuroendocrine, pancreatic, and uveal melanoma liver metastases. A recent meta-analysis demonstrated tumor control rate of 81% following radioembolization for metastatic breast cancer to the liver (Feretis and Solodkyy 2020). Higher radiation dose to tumors has been shown to be associated with improved objective response (Ridouani et al. 2021). A series of 244 patients with neuroendocrine carcinomas treated with radioembolization was reported by Braat et al. Radioembolization resulted in complete response in 8%, partial response in 35%, stable disease in 48%, and progressive disease in 9% according to mRECIST. Lymphocytopenia was the most common adverse event at 6.7%. In symptomatic patients, symptoms improved and resolved in 44% and 34%, respectively. Median overall survival from time of first radioembolization was reported by tumor grade, with 3.7, 2.7, and 0.7 years for G1, G2, and G3 tumors, respectively (Braat et al. 2019). The largest series to date regarding pancreatic liver metastases was described by Kim et al., and included 33 patients with chemotherapy refractory metastatic disease to the liver. Following treatment, 42% had partial response, 37% had stable disease, and 21% had disease progression. Median overall survival from radioembolization was 8.1 months, with median overall survival from diagnosis of 20.8 months (Kim et al. 2016). A single-center retrospective study demonstrated efficacy and safety of radioembolization for treatment of hepatic metastatic disease from uveal melanoma. Gonsalves et al. showed median overall survival of 10.0 months and progression-free survival in the liver of 4.7 months following radioembolization with excellent toxicity profile. Patients with liver tumor burden less than 25% had significantly better overall and progression-free survival (Gonsalves et al. 2011).

Conclusions

Thermal ablation has demonstrated local progression free and overall survival benefits when used alone or in conjunction with other systemic, locoregional, and/or surgical treatments for patients with unresectable metastatic liver disease. For resectable colorectal liver metastases ≤3 cm, retrospective analyses suggest comparable curative potential between heat-based thermal ablation versus surgical resection; prospective randomized clinical trials are currently in progress. Irreversible electroporation is a novel non-thermal ablation method which provides a potentially safer alternative for tumors near major vascular or biliary structures, though has more constraints limiting the ablation zone size compared to thermal ablation options and requires additional investigation into appropriate patient and tumor characteristic selection. Transarterial therapies such as radioembolization are versatile, and can be used to downstage patients to curative resection, induce hypertrophy of the future liver remnant, or palliate patients with unresectable disease. Radioembolization has demonstrated benefit in a variety of cancers.

While standard practice of ablation of metastatic liver tumors may slightly differ from institution to institution, each patient warrants an individual multidisciplinary review to discuss available options including ablation and best next steps.

Key Take Home Messages

- Portal vein embolization with N-butyl cyanoacrylate glue has shown to have the best effect on future liver remnant hypertrophy in recent studies.
- Microwave ablation achieves higher temperatures over a larger zone at a faster rate and is less susceptible to the heat sink effect compared to radiofrequency ablation. Curative intent for ablation is not recommended for tumors >5 cm.
- RAS mutant tumors may be more ablation resistant and require greater margins and/or repeat ablation procedures.
- Yttrium-90 radioembolization can also be used for treatment of colorectal liver metastases with curative intent.

Areas for Further Research

- Hepatic vein embolization has been described in combination with portal vein embolization, which may improve future liver remnant hypertrophy and improve kinetic growth rate.

- Yttrium radiation lobectomy is an alternative to portal vein embolization, but more research is needed comparing these techniques for augmentation of the future liver remnant in patients with liver metastases.
- No randomized data is available comparing radiofrequency to microwave ablation treatment of liver metastases.
- No randomized data is available comparing surgery vs ablation for colorectal liver metastases <3 cm in size; the ongoing COLLISION trial is evaluating this question.

Trusted Links for Further Reading

- Luz JHM, Veloso Gomes F, Costa NV, et al. BestFLR Trial: Liver regeneration at CT before major hepatectomies for liver cancer – A randomized controlled trial comparing portal vein embolization with N-butyl-cyanoacrylate plus iodized oil versus polyvinyl alcohol particles plus coils. Radiology. 2021;299(3):715–724.
- Niekamp AS, Huang SY, Mahvash A, et al. Hepatic vein embolization after portal vein embolization to induce additional liver hypertrophy in patients with metastatic colorectal carcinoma. European Radiology. 2020;30(7):3862–3868.
- Filippiadis DK, Velonakis G, Kelekis A, Sofocleous CT. The Role of Percutaneous Ablation in the Management of Colorectal Cancer Liver Metastatic Disease. Diagnostics. 2021;11(2):308. doi:10.3390/diagnostics11020308.
- Mulcahy MF, Salem R, Mahvash A, et al. LBA21 Radioembolization with chemotherapy for colorectal liver metastases: A randomized, open-label, international, multicenter, phase III trial (EPOCH study). Annals of Oncology. 2021;32:S1295.

Radiation Therapy

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Introduction

Over the past three decades, radiation therapy has been increasingly employed in the treatment of patients with hepatic metastases from colorectal cancer (CRC). This can be attributed in part to innovations in imaging, leading to improved target delineation, as well as advances in the delivery of highly conformal, high-dose radiation therapy, yielding improved local control rates and decreased treatment-related toxicity. There has also been growing interest in metastasis-directed therapy (MDT) as a means to prolong progression-free survival in patients with limited metastatic disease burden. Contemporary randomized studies have also demonstrated the potential for metastasis-directed radiation therapy to improve the overall survival of select patients with oligometastatic disease (Palma et al. 2020). Definitive treatment strategies for liver metastases include stereotactic body radiation therapy (SBRT) and hepatic artery infusion (HAI) of radioactive spheres. Patients with intact liver function who present with a small number of low-volume metastatic liver lesions tend to have excellent control following definitive radiation treatments. On the other end of the spectrum, there are other patients with more advanced metastatic disease involving the liver who may benefit from radiation therapy delivered with palliative intent. This section will review therapeutic methods and results of definitive radiation therapy for liver metastases from CRC as well as palliative radiation for diffuse symptomatic hepatic disease.

Stereotactic Body Radiation Therapy

Historically, external beam radiation therapy was used infrequently in the treatment of liver malignancies secondary to the limited tolerance of the whole liver to radiation (Ben-Josef and Lawrence 2005a). Radiation-induced liver disease (RILD), a syndrome characterized by anicteric hepatomegaly, ascites, and impaired liver function studies, develops in 5% of patients receiving 30–35 Gy to the whole liver. The development of three dimensional (3D) conformal treatment planning permitted treatment of the tumor while minimizing dose to the uninvolved liver and facilitated a quantitative understanding of the relationships of dose, volume, and probability of complication (Ben-Josef and Lawrence 2005a). Initial studies from various institutions demonstrated favorable outcomes for patients treated with small doses of radiation once or twice daily for multiple weeks, sometimes with concurrent systemic therapy for radiosensitization, as is conventional for the treatment of many primary malignancies (Ben-Josef et al. 2005b; Dawson et al. 2000).

Further technological advances have since made it possible to deliver condensed courses of tumoricidal radiation therapy (Kavanagh et al. 2006). Stereotactic body radiation therapy (SBRT) is a treatment technique that allows for precise delivery of ablative radiation to the target, utilizing either a single dose or a small number of fractions. This is in contrast to 3D conformal radiation therapy protocols, which utilize daily or twice-daily low-dose radiation treatments administered over many weeks. SBRT allows for dose escalation to the tumor while maintaining conformality and steep dose fall-off outside of the treatment volume. With this technique, local control rates in excess of 80% have been achieved in select patients with metastases from lung, breast, renal, and other cancers (Kavanagh et al. 2006). The abbreviated treatment course also results in fewer interruptions in the delivery of systemic therapy. The application of SBRT for hepatic metastases was previously handicapped by two problems (Kavanagh et al. 2006). First, tumors in the liver are subject to motion related to respiration. Second, because the treatments are highly focused, it is required that the target extent be confidently and reproducibly defined by diagnostic and treatment planning imaging modalities. Image guidance during therapy is required to ensure that selected patients are properly treated with limited fields and that the target extent can be determined accurately. Over the past 30 years, significant technological advances in defining tumor motion through image guidance have helped overcome these challenges and have permitted the precise treatment of liver metastases (Figures 5 and 6). In select cases radiopaque fiducial markers can also be placed in close proximity to the treatment site to facilitate image-guided radiation delivery.

There is no single agreed-upon radiation dose or fractionation regimen for the treatment of liver metastases. The numerous reported studies of SBRT for liver tumors have included both single- and multi-fraction regimens. A multicenter study from the University of Colorado, University of Texas-Southwestern, and University of Indiana reported the results of one of the earliest phase I trials of SBRT for liver metastases (Schefter et al. 2005). Eligible patients had one to three liver metastases, tumor diameter < 6 cm, and adequate liver function. The first patient cohort received 36 Gy delivered over three fractions to the target volume. Subsequent cohorts received progressively higher doses up to a maximum of 60 Gy in three fractions. Eighteen patients were enrolled and the most common primary site was colorectal cancer. No patients experienced dose-limiting toxicity and dose was escalated to 60 Gy in three fractions without reaching the maximum tolerated dose. During the phase II portion of the trial, 47 patients with 63 lesions were treated with 60 Gy in three fractions. The investigators reported a two-year actuarial local control rate of 92% for the cohort at large, with superior local control rates noted for smaller tumors (100% for tumors < 3 cm vs 77% for tumors >3 cm). Only one patient experienced a grade 3 or higher toxicity, and the importance of limiting the mean dose to uninvolved liver to <15 Gy in order to minimize

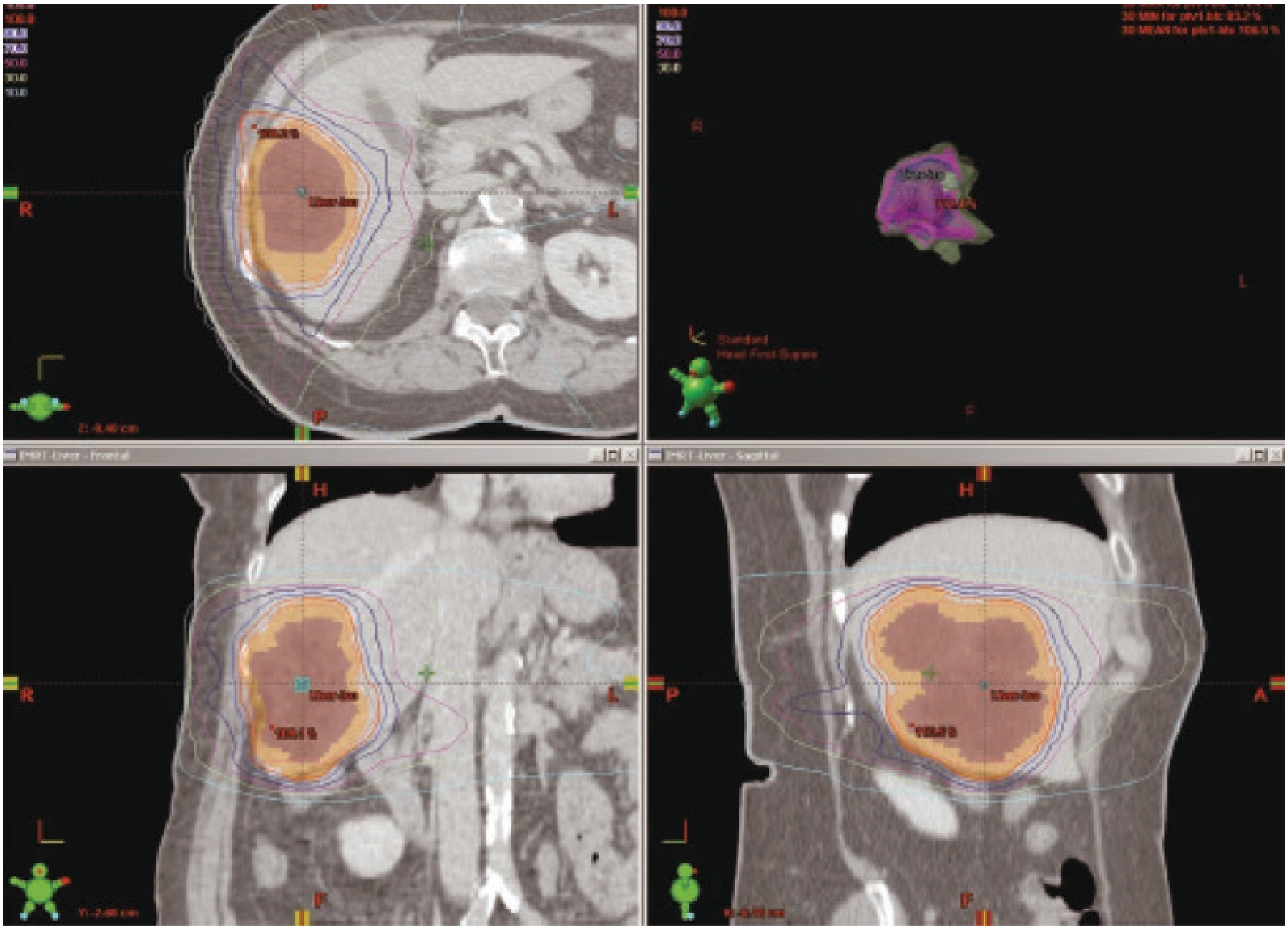

Figure 5 Axial, sagittal, coronal radiation isodose distribution of stereotactic treatment of hepatic metastasis. Colored lines represent relative doses of radiation around gross tumor volume (GTV) (located centrally; brown color wash) and planning target volume (PTV) (accounting for physiologic motion and subclinical disease extension; orange color wash).

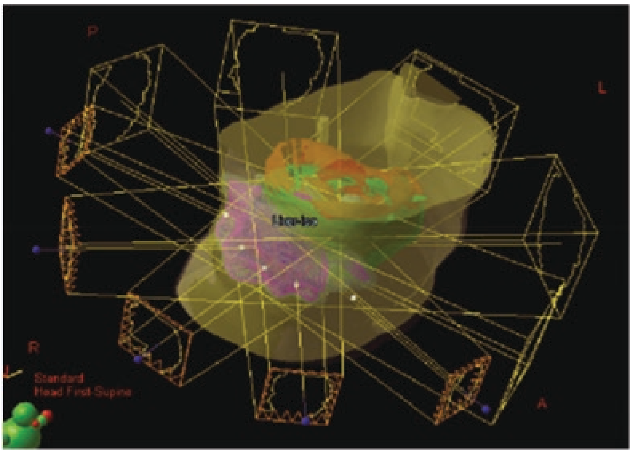

Figure 6 Radiation beam field arrangements of stereotactic body radiation therapy for hepatic metastasis.

the risk of RILD was demonstrated (Rusthoven et al. 2009). The authors concluded that biologically potent doses of SBRT are well-tolerated and efficacious in the treatment of patients with liver metastases. Dose-response and size-response relationships have subsequently been confirmed by numerous other studies investigating SBRT for liver lesions. Lee et al. conducted a phase I study of SBRT for inoperable liver metastases, enrolling 68 patients, 40 of whom had colorectal primaries. Median prescription dose was 41.4 Gy in six fractions and 87% of patients had disease that was refractory to at least one line of chemotherapy. The one-year local control rate was 71%, with significantly improved local control rates again noted in smaller volume tumors (<75.2 mL) and when higher dose was able to be delivered (Lee et al. 2009). In a multi-institutional pooled analysis of 65 patients with 1–4 liver metastases from colorectal primaries treated with SBRT in 1–6 fractions, Chang et al. demonstrated that BED_{10}>117 Gy (equivalent to 46–52 Gy in three fractions) is required to achieve one-year local control rates of >90% and is associated with improved overall survival. The authors additionally demonstrated that presence of active extrahepatic disease was associated with decreased overall survival (Chang et al. 2011). Other studies have validated a clear dose-response relationship when treating liver metastases from colorectal cancer, and in doing so have also hinted at the relative radio-resistance of this particular histology (Ahmed et al. 2016; Joo et al. 2017; McPartlin et al. 2017). The typical recommendation is to achieve a BED_{10} dose of at least 100 Gy when possible, with acknowledgment that larger lesions may require even further dose escalation. Unfortunately, dose escalation can sometimes be limited by nearby normal tissue tolerance. The primary dose-limiting structures are typically the uninvolved liver and nearby luminal gastrointestinal structures such as bowel and stomach. There are a wide variety of acceptable dose constraints, none of which arguably are supported by high-level evidence, thus the clinical picture and the technical expertise of the treating physicians and institutions must be relied upon heavily in order to strike the right balance between treatment efficacy and safety (Miften et al. 2021). Toxicity rates from numerous prospective and retrospective studies have notably been low; rates of acute grade 3 or higher toxicities are typically less than 10%, when reasonable normal tissue constraints are respected (Mohamad et al. 2022).

While there is currently no published phase III randomized controlled data on the use of SBRT for liver metastases from colorectal cancer, long-term phase I/II prospective data supporting SBRT for liver metastases are emerging. A phase II prospective trial of SBRT for patients with unresectable oligometastatic liver lesions reported excellent five-year local control rates of 78% (Scorsetti et al. 2018). The investigators enrolled 61 patients, 29 of whom had colorectal primaries, and treated 76 lesions with 75 Gy in three fractions, allowing for dose reduction per protocol. All patients had 1–3 liver metastases; slightly less than half of the patients had lesions > 3 cm, and nearly half of the patients had received local therapies for their liver metastases previously. Data such as these have led to an update of ESMO consensus guidelines for the management of patients with metastatic colorectal cancer to include SBRT as a safe and feasible treatment for patients who are not surgical candidates (Van Cutsem et al. 2016).

Advances in SBRT technology that are currently under investigation include the use of proton beam therapy, which allows for a steep exit-dose gradient beyond the target. This modality can potentially limit the dose to nearby normal structures, most notably the uninvolved liver, and thereby theoretically decrease treatment-related toxicity. Hong et al. enrolled 89 patients with liver metastases, the majority of whom had a colorectal primary, into a single institution phase II study investigating the safety and efficacy of proton-based SBRT. Enrolled patients had limited extrahepatic disease, at least 800 mL of uninvolved liver, relatively intact liver function, and 1–4 liver metastases. They were treated with 30–50 GyE in 5 fractions. Three-year local control was 61.2%. The authors interestingly noted that patients with mutations in the KRAS and/or TP53 oncogenes had particularly radioresistant tumors, with 1-year local control rates of only 20%. No grade 3 or higher toxicities were reported. The authors concluded that proton beam therapy was well-tolerated and effective in the treatment of liver metastases (Hong et al. 2017). Further study is indicated, as proton beam therapy could emerge as an important toxicity-limiting modality, particularly in the setting of dose escalation and in the salvage or re-irradiation setting. MR-guided liver SBRT is also under active prospective investigation, with the purported benefits including increased sensitivity of tumor targeting, allowing for further dose escalation to the tumor and improved avoidance of normal structures.

In summary, based on the available data, SBRT has emerged as a safe and effective ablative therapy for patients with metastatic liver lesions from CRC. At this time, patients who are ideal candidates for SBRT to liver metastases from CRC are primarily those who are not suitable for resection, as surgery remains the gold standard for local therapy, and there have been no head-to-head prospective comparisons between surgery and SBRT. Other ideal patient/treatment characteristics based on available data include a small volume of liver metastases in terms of both size and number or lesions; lack of extrahepatic metastases; relatively intact liver function; limited prior systemic therapy; and lack of proximity to luminal gastrointestinal tissues. The decision whether to and with what dose/fractionation to treat is highly individualized based on these factors, as they are relevant for treatment efficacy, oncologic outcomes, and also patient safety. Genetic testing may further inform this decision-making process in the future, though further prospective study is required. In terms of comparison to other ablative therapies, there are ongoing prospective trials comparing SBRT to MWA for the treatment of liver metastases. As discussed previously, the use of RFA is usually limited by lesion size as well as proximity to the biliary tree and blood vessels, whereas SBRT can sometimes be more effectively administered in these circumstances (Jackson et al. 2018).

Yttrium-90

As mentioned above under “Interventional Radiology – Radioembolization,” resin microspheres containing Yttrium-90 (Y90), a high energy beta-emitting isotope, have been used in the treatment of patients with hepatic metastases from colorectal cancer (Kennedy et al. 2006; Lim et al. 2005). The yttrium resin microspheres are embolized into the hepatic artery where they become lodged within the tumor microvasculature. The treatment is relatively selective as hepatic tumors derive their blood supply almost exclusively from the hepatic artery whereas normal liver parenchyma is supplied by the portal circulation. Animal studies suggest that the yttrium microspheres allow on average 200–300 Gy to be delivered to liver tumors. Appropriate patient selection is again a hallmark of treatment efficacy and safety. Patients with limited extrahepatic disease and adequate liver function are preferred candidates. As with SBRT, radiation-induced liver disease (RILD) carries potential treatment-related toxicity.

Hendlisz et al. enrolled 46 patients with unresectable, chemotherapy-refractory liver-only metastatic colorectal cancer into a prospective multicenter randomized phase III trial comparing continuous 5-FU infusion alone to continuous 5-FU with radioembolization. The primary endpoint was time to liver progression, which was 2.1 months in the chemotherapy-alone arm, in comparison to 5.5 months with the addition of radioembolization (p = 0.03). There was no significant difference in treatment-related toxicities between the two arms. The authors concluded that Y90 radioembolization was well tolerated and is a valid therapeutic option for this subset of patients (Hendlisz et al. 2010).

There have since been three multicenter randomized phase III trials conducted investigating the efficacy of combining first-line chemotherapy with Y90 radio-embolization in patients with colorectal cancer with liver metastases not suitable for resection or ablation: FOXFIRE, SIRFLOX, and FOXFIRE-Global (Wasan et al. 2017). A combined analysis of the three trials, with >500 patients per arm, revealed no improvement in overall survival or progression-free survival with the addition of Y90 radioembolization to first-line FOLFOX chemotherapy, with median follow up of 43.3 months. Thus, early use of Y90 radioembolization in combination with chemotherapy for patients with liver-only or liver-dominant metastatic colorectal cancer cannot be recommended at this time (Wasan et al. 2017), though further study of Y90 radioembolization as a consolidative treatment after chemotherapy could be considered. A more recent prospective trial randomized 428 patients with colorectal liver metastases who had progressed on first line therapy to second line chemotherapy, with or without radioembolization. The hazard ratio for progression-free survival was 0.69 (P = 0.0013) with a median progression-free survival of 8 vs. 7.2 months, favoring radioembolization. Similarly, the hazard ratio for hepatic progression-free survival was 0.59 (P = <0.001) with a median hepatic progression-free survival of 9.1 vs. 7.2 months although median overall survival was 14 vs. 14.4 months (P = NS). Grade III adverse events were seen more frequently in the radioembolization group (68% vs. 49%). The authors concluded the addition of radioembolization to second-line chemotherapy led to a longer progression-free and hepatic progression-free survival, although subset analyses are needed to better define the ideal patient population to benefit such (Mulcahy et al. 2021a).

Palliative External Beam Radiation Therapy

Patients can be exquisitely symptomatic from large-burden hepatic metastatic disease, including disease adjacent to/involving the hepatic capsule with painful distention. Whole liver radiation therapy has been studied as a means of palliation for patients who are not candidates for alternative therapies including SBRT or Y90 radioembolization, typically in the setting of extensive metastatic intra- and/or extra-hepatic disease, or poor underlying liver function. A historical trial from the Radiation Therapy Oncology Group prospectively enrolled 109 patients with hepatic metastases to receive a variety of hepatic radiation doses ranging from 21–30 Gy over 7–15 fractions. No documented cases of radiation-induced hepatitis were appreciated, with symptomatic improvement rates ranging from 19% (weakness/fatigue) to 55% (pain). An improvement in liver function chemistries was seen in 40%, along with improvement in performance status in 25%. The authors concluded that rapid courses of whole liver radiation were well tolerated with good therapeutic benefit in patients with symptomatic liver metastases (Borgelt et al. 1981). Although conventional fractionation has previously been studied, courses of more condensed duration are currently being actively investigated due to patient convenience and minimized interruptions to systemic therapy. A prospective trial examining the efficacy and tolerability of 10 Gy in two fractions to partial/whole liver for palliation of symptomatic liver metastases was undertaken by Bydder et al. These investigators enrolled 28 patients, ~40% of whom had metastatic colorectal cancer, and the majority of whom had not been palliated by previous chemotherapy or high dose steroids. The authors reported symptom response rate of 53–66% at 2 weeks post-treatment and only 7% of patients experiencing grade 3 or higher acute toxicity (Bydder et al. 2003). A more recent phase II trial enrolled patients with symptomatic hepatocellular carcinoma or solid tumor liver metastases unsuitable for alternate therapies. The patients were treated with 8 Gy in one fraction to 75–100% of the liver using anterior-posterior opposed or oblique beams, with premedication with anti-emetics and steroids. Forty-one patients were accrued, 20 of whom had liver metastases. Approximately half of the accrued patients experienced an improvement in symptoms within a month, with approximately one quarter of patients noting improved quality of life. Only one patient developed a grade 3 toxicity (nausea), and this patient declined pre-medication (Soliman et al. 2013). A phase III study is randomizing patients with symptomatic diffuse multifocal hepatocellular carcinoma or liver metastases refractory to or unsuitable for standard systemic/targeted therapies to single fraction palliative radiation therapy to the whole liver + best supportive care vs best supportive care alone (NCT02511522).

Conclusion

Recent technological advances in radiation therapy have provided the means to deliver tumoricidal doses of radiation therapy to patients with inoperable colorectal cancer metastases to the liver. These techniques include stereotactic body radiation therapy, and hepatic artery infusion of radioactive spheres. Data employing stereotactic body radiation therapy are for the most part limited to phase I and II trials; however, utilization has become more commonplace as the data matures. External beam radiation therapy also has an ongoing role in the palliation of patients with large burden, symptomatic, metastatic hepatic disease, with an ongoing phase III clinical trial investigating the benefit of its addition to best supportive care. We await the results of future prospective studies and further delineation of appropriate patient selection for these definitive modalities.

Key Take Home Messages

- Stereotactic body radiation therapy for the treatment of unresectable colorectal liver metastases has demonstrated high rates of prolonged local control with low toxicity in phase I/II trials.
- Randomized trials do not support the use of Yttrium-90 radioembolization in combination with first-line systemic chemotherapy for patients with liver-only or liver-dominant metastatic colorectal cancer.

Areas for Further Research

- Proton beam therapy can potentially limit the dose to nearby normal structures, including the uninvolved liver.
- Yttrium-90 for the treatment of colorectal liver metastases after first-line chemotherapy may be beneficial for subsets of patients.
- Whole liver radiation therapy may be beneficial for patients with liver metastases refractory or unsuitable for other systemic and targeted therapies; a phase III randomized trial to study this is ongoing.

Trusted Links for Further Reading

- Scorsetti M, Comito T, Clerici E, et al. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after five years of follow-up. Radiat Oncol. Nov 26 2018;13(1):234. doi:10.1186/s13014-018–1185-9.
- Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 09 2017;18(9):1159–1171. doi:10.1016/S1470-2045(17)30457–6.
- Soliman H, Ringash J, Jiang H, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. J Clin Oncol. Nov 01 2013;31(31):3980–6. doi:10.1200/JCO.2013.49.9202.

References

Abulkhir, A., Limongelli, P., Healey, A.J. et al. (2008). Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 247 (1): 49–57.

Ahmed, K.A., Caudell, J.J., El-Haddad, G. et al. (2016). Radiosensitivity differences between liver metastases based on primary histology suggest implications for clinical outcomes after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 95 (5): 1399–1404.

Akhurst, T., Kates, T.J., Mazumdar, M. et al. (2005). Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. *J Clin Oncol* 23 (34): 8713–8716.

Alberts, S.R., Roh, M.S., Mahoney, M.R. et al. (2010). ‘Alternating systemic and hepatic artery infusion therapy for resected liver metastases from colorectal cancer: a North Central Cancer Treatment Group (NCCTG)/ National Surgical Adjuvant Breast and Bowel Project (NSABP) phase II intergroup trial, N9945/CI-66′. *J Clin Oncol* 28 (5): 853–858.

Ali, A., Ahle, M., Björnsson, B., and Sandström, P. (2021). Portal vein embolization with N-butyl cyanoacrylate glue is superior to other materials: a systematic review and meta-analysis. *Eur Radiol* 31 (8): 5464–5478.

Andre, T., Shiu, K.K., Kim, T.W. et al. (2020). Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med* 383 (23): 2207–2218.

Andreou, A., Brouquet, A., Abdalla, E.K. et al. (2011). Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. *HPB* 13 (11): 774–782.

Archer, S.G. and Gray, B.N. (1989). Vascularization of small liver metastases. *Br J Surg* 76 (6): 545–548.

Ardito, F., Razionale, F., Salvatore, L. et al. (2021). Discordance of KRAS mutational status between primary tumors and liver metastases in colorectal cancer: impact on long-term survival following radical resection. *Cancers* 13 (9): 2148.

Azoulay, D., Castaing, D., Smail, A. et al. (2000). Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg* 231 (4): 480.

Ballantyne, G.H. and Quin, J. (1993). Surgical treatment of liver metastases in patients with colorectal cancer. *Cancer* 71 (12 Suppl): 4252–4266.

Bartolozzi, C. and Lencioni, R. (1996). Ethanol injection for the treatment of hepatic tumours. *Eur Radiol* 6 (5): 682–696.

Baumgart, J., Lang, S., and Lang, H. (2011). A new method for induction of liver hypertrophy prior to right trisectionectomy: a report of three cases. *hPb (Oxford)* 13 (Suppl 2): 71–72.

Bekki, Y., Marti, J., Toshima, T. et al. (2021). A comparative study of portal vein embolization versus radiation lobectomy with Yttrium-90 micropheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. *Surgery* 169 (5): 1044–1051.

Belli, G., D'Agostino, A., Ciciliano, F. et al. (2002). Liver resection for hepatic metastases: 15 years of experience. *J Hepatobiliary Pancreat Surg* 9 (5): 607–613.

Bengmark, S. and Hafstrom, L. (1969). The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. *Cancer* 23 (1): 198–202.

Bengtsson, G., Carlsson, G., Hafstrom, L., and Jonsson, P.E. (1981). Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 141 (5): 586–589.

Ben-Josef, E. and Lawrence, T.S. (2005a). Radiotherapy for unresectable hepatic malignancies. *Semin Radiat Oncol* 15 (4): 273–278.

Ben-Josef, E., Normolle, D., Ensminger, W.D. et al. (2005b). Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. *J Clin Oncol* 23 (34): 8739–8747.

Bertot, L.C., Sato, M., Tateishi, R. et al. (2011). Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol* 21 (12): 2584–2596.

Bilchik, A.J. (2000). Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms. *Arch Surg* 135 (6): 657.

Bokemeyer, C., Bondarenko, I., Makhson, A. et al. (2009). Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 27 (5): 663–671.

Borgelt, B.B., Gelber, R., Brady, L.W. et al. (1981). The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. *Int J Radiat Oncol Biol Phys* 7 (5): 587–591.

Braat, A.J., Kappadath, S.C., Ahmadzadehfar, H. et al. (2019). Radioembolization with 90Y resin microspheres of neuroendocrine liver metastases: international multicenter study on efficacy and toxicity. *Cardiovascular Intervent Radiol* 42 (3): 413–425.

Breedis, C. and Young, G. (1954). The blood supply of neoplasms in the liver. *Am J Pathol* 30 (5): 969–977.

Bridgewater, J.A., Pugh, S.A., Maishman, T. et al. (2020). Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 21 (3): 398–411.

Busuttil, A. (1974). Ectopic adrenal within the gall-bladder wall. *J Pathol* 113 (4): 231–233.

Butte, J.M., Gönen, M., Allen, P.J. et al. (2015). Recurrence after partial hepatectomy for metastatic colorectal cancer: potentially curative role of salvage repeat resection. *Ann Surg Oncol* 22 (8): 2761–2771.

Bydder, S., Spry, N.A., Christie, D.R. et al. (2003). A prospective trial of short-fractionation radiotherapy for the palliation of liver metastases. *Australas Radiol* 47 (3): 284–288.

Calandri, M., Yamashita, S., Gazzera, C. et al. (2018). Ablation of colorectal liver metastasis: interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. *Eur Radiol* 28 (7): 2727–2734.

Cannon, R., Ellis, S., Hayes, D. et al. (2013). Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. *J Surg Oncol* 107 (5): 544–549.

Chang, D.T., Swaminath, A., Kozak, M. et al. (2011). Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer* 117 (17): 4060–4069.

Cheung, T.T., Ma, K.W., and She, W.H. (2021). A review on radiofrequency, microwave and high-intensity focused ultrasound ablations for hepatocellular carcinoma with cirrhosis. *Hepatobiliary Surg Nutr* 10 (2): 193–209.

Choi, J.-Y., Lee, J.-M., and Sirlin, C.B. (2014). CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects. *Radiology* 272 (3): 635–654.

Choti, M.A., Sitzmann, J.V., Tiburi, M.F. et al. (2002). Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 235 (6): 759–766.

Clavien, P.-A., Petrowsky, H., DeOliveira, M.L., and Graf, R. (2007). Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 356 (15): 1545–1559.

Colucci, G., Gebbia, V., Paoletti, G. et al. (2005). Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 23 (22): 4866–4875.

Coppa, G.F., Eng, K., Ranson, J.H. et al. (1985). Hepatic resection for metastatic colon and rectal cancer. An evaluation of preoperative and postoperative factors. *Ann Surg* 202 (2): 203–208.

Cornelis, F.H., Durack, J.C., Kimm, S.Y. et al. (2017). A comparative study of ablation boundary sharpness after percutaneous radiofrequency, cryo-, microwave, and irreversible electroporation ablation in normal swine liver and kidneys. *Cardiovasc Intervent Radiol* 40 (10): 1600–1608.

Creasy, J.M., Sadot, E., Koerkamp, B.G. et al. (2018a). Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? *Surgery* 163 (6): 1238–1244.

Creasy, J.M., Sadot, E., Koerkamp, B.G. et al. (2018b). The impact of primary tumor location on long-term survival in patients undergoing hepatic resection for metastatic colon cancer. *Ann Surg Oncol* 25 (2): 431–438.

Cremolini, C., Antoniotti, C., Rossini, D. et al. (2020a). Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 21 (4): 497–507.

Cremolini, C., Antoniotti, C., Rossini, D. et al. (2020b). Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 21 (4): 497–507.

Crocetti, L., De Baére, T., Pereira, P.L., and Tarantino, F.P. (2020). CIRSE standards of practice on thermal ablation of liver tumours. *Cardiovasc Intervent Radiol* 43 (7): 951–962.

Cunha, M., Barros, I., Marreiros, A. et al. (2019). Futility and utility of two-stage hepatectomy. *Ann Oncol* 30: iv68.

Cunningham, D., Humblet, Y., Siena, S. et al. (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351 (4): 337–345.

D'Angelica, M.I., Correa-Gallego, C., Paty, P.B. et al. (2015). Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. *Ann Surg* 261 (2): 353–360.

Davalos, R.V., Mir, L.M., and Rubinsky, B. (2005). Tissue ablation with irreversible electroporation. *Ann Biomed Eng* 33 (2): 223–231.

Dawson, L.A., McGinn, C.J., Normolle, D. et al. (2000). Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. *J Clin Oncol* 18 (11): 2210–2218.

de Graaf, W., van den Esschert, J.W., van Lienden, K.P., and van Gulik, T.M. (2009). Induction of tumor growth after preoperative portal vein embolization: is it a real problem? *Ann Surg Oncol* 16 (2): 423–430.

de Gramont, A., Figer, A., Seymour, M. et al. (2000). Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18 (16): 2938–2947.

DeMatteo, R.P., Palese, C., Janmgin, W.R. et al. (2000). Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg* 4 (2): 178–184.

Demetri, G.D., De Braud, F., Drilon, A. et al. (2022). Updated integrated analysis of the efficacy and safety of entrectinib in patients with NTRK fusion-positive solid tumors. *Clin Cancer Res* 28 (7): 1302–1312.

Dhir, M., Jones, H.L., Shuai, Y. et al. (2017). Hepatic arterial infusion in combination with modern systemic chemotherapy is associated with improved survival compared with modern systemic chemotherapy alone in patients with isolated unresectable colorectal liver metastases: a case-control study. *Ann Surg Oncol* 24 (1): 150–158.

Dixon, M., Cruz, J., Sarwani, N., and Gusani, N. (2021). The future liver remnant: definition, evaluation, and management. *Am Surg* 87 (2): 276–286.

Doci, R., Gennari, L., Bignami, P. et al. (1991). One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. *Br J Surg* 78 (7): 797–801.

Dorcaratto, D., Mazzinari, G., Fernandez, M. et al. (2019). Impact of postoperative complications on survival and recurrence after resection of colorectal liver metastases: systematic review and meta-analysis. *Ann Surg* 270 (6): 1018–1027.

Douillard, J.Y., Cunningham, D., Roth, A.D. et al. (2000). Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 355 (9209): 1041–1047.

Douillard, J.-Y., Oliner, K.S., Siena, S. et al. (2013). Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 369 (11): 1023–1034.

Dueland, S., Guren, T.K., Hagness, M. et al. (2015). Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? *Ann Surg* 261 (5): 956–960.

Dupré, A., Jones, R.P., Diaz-Nieto, R. et al. (2017). Curative-intent treatment of recurrent colorectal liver metastases: a comparison between ablation and resection. *Eur J Surg Oncol* 43 (10): 1901–1907.

Ekberg, H., Tranberg, K.G., Andersson, R. et al. (1987). Pattern of recurrence in liver resection for colorectal secondaries. *World J Surg* 11 (4): 541–547.

Elias, D., Lasser, P., Hoang, J.M. et al. (1993). Repeat hepatectomy for cancer. *Br J Surg* 80 (12): 1557–1562.

Emmons, E.C., Bishay, S., Du, L. et al. (2022 October). Survival and toxicities after 90Y transarterial radioembolization of metastatic colorectal cancer in the RESIN Registry. *Radiology* 305 (1): 228–236. doi: 10.1148/radiol.220387. Epub 2022 Jun 28. PMID: 35762890.

Ensminger, W., Niederhuber, J., Dakhil, S. et al. (1981). Totally implanted drug delivery system for hepatic arterial chemotherapy. *Cancer Treat Rep* 65 (5–6): 393–400.

Ensminger, W.D., Rosowsky, A., Raso, V. et al. (1978). A clinical-pharmacological evaluation of hepatic arterial infusions of 5-fluoro-2′-deoxyuridine and 5-fluorouracil. *Cancer Res* 38 (11 Pt 1): 3784–3792.

Entezari, P., Gabr, A., Kennedy, K. et al. (2021 October). Radiation lobectomy: an overview of concept and applications, technical considerations, outcomes. *Sem Intervent Radiol* 38 (4): 419–424. doi: 10.1055/s-0041-1735530. Epub 2021 Oct 7. PMID: 34629708; PMCID: PMC8497080.

Eovist (gadoxetate disodium) solution label - Accessdata.fda.gov (2010). United States Food and Drug Administration.

Erinjeri, J.P. and Clark, T.W.I. (2010). Cryoablation: mechanism of action and devices. *J Vasc Interv Radiol* 21 (8): S187–S191.

Fan, -X.-X., Lv, S.-Y., Zhang, M.-W. et al. (2020). Clinical analysis of ultrasound-guided radiofrequency ablation for recurrent colorectal liver metastases after hepatectomy. *World J Surg Oncol* 18: 1.

Feretis, M. and Solodkyy, A. (2020). Yttrium-90 radioembolization for unresectable hepatic metastases of breast cancer: a systematic review. *World J Gastrointest Oncol* 12 (2): 228.

Filippiadis, D.K., Velonakis, G., Kelekis, A., and Sofocleous, C.T. (2021). The role of percutaneous ablation in the management of colorectal cancer liver metastatic disease. *Diagnostics* 11 (2): 308.

Folprecht, G., Gruenberger, T., Bechstein, W.O. et al. (2010). Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 11 (1): 38–47.

Fong, Y. and Blumgart, L.H. (1997). Useful stapling techniques in liver surgery. *J Am Coll Surg* 185 (1): 93–100.

Fong, Y., Blumgart, L.H., Cohen, A. et al. (1994). Repeat hepatic resections for metastatic colorectal cancer. *Ann Surg* 220 (5): 657–662.

Fong, Y., Fortner, J., Sun, R.L. et al. (1999). Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 230 (3): 309–318; discussion 318-21.

Fong, Y., Gonen, M., Rubin, D. et al. (2005). Long-term survival is superior after resection for cancer in high-volume centers. *Ann Surg* 242 (4): 540–544; discussion 544-7.

Foster, J.H. (1978). Survival after liver resection for secondary tumors. *Am J Surg* 135 (3): 389–394.

Francica, G. (2017). Needle track seeding after radiofrequency ablation for hepatocellular carcinoma: prevalence, impact, and management challenge. *J Hepatocell Carcinoma* 4: 23–27.

Fuchs, C.S., Marshall, J., Mitchell, E. et al. (2007). Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 25 (30): 4779–4786.

Fukami, Y., Kaneoka, Y., Maeda, A. et al. (2017). Postoperative complications following aggressive repeat hepatectomy for colorectal liver metastasis have adverse oncological outcomes. *Surg Today* 47 (1): 99–107.

Gaba, R.C., Lewandowski, R.J., Kulik, L.M. et al. (2009). Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. *Ann Surg Oncol* 16 (6): 1587–1596.

Gabr, A., Polineni, P., Mouli, S.K. et al. (2019 May). Neoadjuvant radiation lobectomy as an alternative to portal vein embolization in hepatocellular carcinoma. *Sem Nucl Med* 49 (3): 197–203. doi: 10.1053/j.semnuclmed.2019.01.009. Epub 2019 Feb 7. PMID: 30954185.

Gagnière, J., Dupré, A., Gholami, S.S. et al. (2020). Is hepatectomy justified for BRAF mutant colorectal liver metastases?: a multi-institutional analysis of 1497 patients. *Ann Surg* 271 (1): 147–154.

Garlipp, B., de Baere, T., Damm, R. et al. (2014). Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. *Hepatology* 59 (5): 1864–1873.

Giacchetti, S., Perpoint, B., Zidani, R. et al. (2000). Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 18 (1): 136–147.

Gillams, A., Goldberg, N., Ahmed, M. et al. (2015). 'Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the interventional oncology sans frontières meeting 2013′. *Eur Radiol* 25 (12): 3438–3454.

Gluck, W.L., Akwari, O.E., Kelvin, F.M., and Goodwin, B.J. (1985). A reversible enteropathy complicating continuous hepatic artery infusion chemotherapy with 5-fluoro-2-deoxyuridine. *Cancer* 56 (10): 2424–2427.

Goldberg, R.M., Sargent, D.J., Morton, R.F. et al. (2004). A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22 (1): 23–30.

Gonsalves, C.F., Eschelman, D.J., Sullivan, K.L. et al. (2011). Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. *Am J Roentgenol* 196 (2): 468–473.

Görgec, B., Hansen, I., Kemmerich, G. et al. (2021). Clinical added value of MRI to CT in patients scheduled for local therapy of colorectal liver metastases (CAMINO): study protocol for an international multicentre prospective diagnostic accuracy study. *BMC Cancer* 21: 1.

Gorgen, A., Muaddi, H., Zhang, W. et al. (2018). The new era of transplant oncology: liver transplantation for nonresectable colorectal cancer liver metastases. *Can J Gastroenterol Hepatol* (2018): 1–7.

Granata, V., Fusco, R., De Lutio Di Castelguidone, E. et al. (2019). Diagnostic performance of gadoxetic acid–enhanced liver MRI versus multidetector CT in the assessment of colorectal liver metastases compared to hepatic resection. *BMC Gastroenterol* 19 (1).

Groot Koerkamp, B., Sadot, E., Kemeny, N.E. et al. (2017). Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: a propensity score analysis. *J Clin Oncol* 35 (17): 1938–1944.

Grothey, A., Van Cutsem, E., Sobrero, A. et al. (2013). Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 381 (9863): 303–312.

Gruttadauria, S., Luca, A., Mandala, L. et al. (2006). Sequential preoperative ipsilateral portal and arterial embolization in patients with colorectal liver metastases. *World J Surg* 30 (4): 576–578.

Guiu, B., Chevallier, P., Denys, A. et al. (2016). Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique. *Eur Radiol* 26 (12): 4259–4267.

Guo, Y., Shi, M., Shen, X. et al. (2014). Capecitabine plus irinotecan versus 5-FU/leucovorin plus irinotecan in the treatment of colorectal cancer: a meta-analysis. *Clin Colorectal Cancer* 13 (2): 110–118.

Guo, Y., Xiong, B.H., Zhang, T. et al. (2016). XELOX vs. FOLFOX in metastatic colorectal cancer: an updated meta-analysis. *Cancer Invest* 34 (2): 94–104.

Hackl, C., Neumann, P., Gerken, M. et al. (2014). Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. *BMC Cancer* 14 (1): 810.

Hagness, M., Foss, A., Line, P.-D. et al. (2013). Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 257 (5): 800–806.

Haller, D.G., Cassidy, J., Clarke, S.J. et al. (2008). Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 26 (13): 2118–2123.

Hallet, J., Sa Cunha, A., Adam, R. et al. (2016). Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg* 103 (10): 1366–1376.

Hecht, J.R., Mitchell, E., Chidiac, T. et al. (2009). A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 27 (5): 672–680.

Hemming, A.W., Reed, A.I., Howard, R.J. et al. (2003). Preoperative portal vein embolization for extended hepatectomy. *Ann Surg* 237 (5): 686–691; discussion 691-3.

Hendlisz, A., Van den Eynde, M., Peeters, M. et al. (2010). Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol* 28 (23): 3687–3694.

Hoekstra, L.T., van Lienden, K.P., Doets, A. et al. (2012). Tumor progression after preoperative portal vein embolization. *Ann Surg* 256 (5): 812–818.

Hoekstra, L.T., van Lienden, K.P., Verheij, J. et al. (2013). Enhanced tumor growth after portal vein embolization in a rabbit tumor model. *J Surg Res* 180 (1): 89–96.

Hohenberger, P., Schlag, P., Schwarz, V., and Herfarth, C. (1990). Tumor recurrence and options for further treatment after resection of liver metastases in patients with colorectal cancer. *J Surg Oncol* 44 (4): 245–251.

Holch, J.W., Ricard, I., Stintzing, S. et al. (2018). Relevance of liver-limited disease in metastatic colorectal cancer: subgroup findings of the FIRE-3/AIO KRK0306 trial. *Int J Cancer* 142 (5): 1047–1055.

Hong, D.S., DuBois, S.G., Kummar, S. et al. (2020). Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 21 (4): 531–540.

Hong, K. and Georgiades, C. (2010). Radiofrequency ablation: mechanism of action and devices. *J Vasc Interv Radiol* 21 (8 Suppl): S179–86.

Hong, T.S., Wo, J.Y., Borger, D.R. et al. (2017). Phase II study of proton-based stereotactic body radiation therapy for liver metastases: importance of tumor genotype. *J Natl Cancer Inst* 109: 9.

House, M.G., Ito, H., Gönen, M. et al. (2010). Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg* 210 (5): 744–752.

Hughes, K., Scheele, J., and Sugarbaker, P.H. (1989). Surgery for colorectal cancer metastatic to the liver. Optimizing the results of treatment. *Surg Clin North Am* 69 (2): 339–359.

Hughes, K.S., Simon, R., Songhorabodi, S. et al. (1986). Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 100 (2): 278–284.

Hurwitz, H., Fehrenbacher, L., Novotny, W. et al. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350 (23): 2335–2342.

Hurwitz, H.I., Tebbutt, N.C., Kabbinavar, F. et al. (2013). Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *Oncologist* 18 (9): 1004–1012.

Hwang, S., Ha, T.-Y., Ko, G.-Y. et al. (2015). Preoperative sequential portal and hepatic vein embolization in patients with hepatobiliary malignancy. *World J Surg* 39 (12): 2990–2998.

Imai, K., Allard, M.A., Castro Benitez, C. et al. (2017). Long-term outcomes of radiofrequency ablation combined with hepatectomy compared with hepatectomy alone for colorectal liver metastases. *Br J Surg* 104 (5): 570–579.

Ituarte, P.H.G., Nelson, R., O'Leary, M.P. et al. (2022 July). Age-adjusted incidence rates of synchronous liver metastases for stage IV colorectal cancer compared by sex, race, and age group. *HPB (Oxford)* 24 (7): 1074–1081. doi: 10.1016/j.hpb.2021.11.017. Epub 2021 Dec 3. PMID: 34924290.

Izzo, F., Granata, V., Grassi, R. et al. (2019). Radiofrequency ablation and microwave ablation in liver tumors: an update. *Oncologist* 24 (10): e990–e1005.

Jackson, W.C., Tao, Y., Mendiratta-Lala, M. et al. (2018). Comparison of stereotactic body radiation therapy and radiofrequency ablation in the treatment of intrahepatic metastases. *Int J Radiat Oncol Biol Phys* 100 (4): 950–958.

Jakobs, T.F., Hoffmann, R.-T., Dehm, K. et al. (2008). Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. *J Vasc Interv Radiol* 19 (8): 1187–1195.

Jamison, R.L., Donohue, J.H., Nagorney, D.M. et al. (1997). Hepatic resection for metastatic colorectal cancer results in cure for some patients. *Arch Surg* 132 (5): 505–510; discussion 511.

Joo, J.H., Park, J.H., Kim, J.C. et al. (2017). Local control outcomes using stereotactic body radiation therapy for liver metastases from colorectal cancer. *Int J Radiat Oncol Biol Phys* 99 (4): 876–883.

Kan, Z. and Madoff, D.C. (2008 June). Liver anatomy: microcirculation of the liver. *Semin Intervent Radiol* 25 (2): 77–85. doi: 10.1055/s-2008-1076685. PMID: 21326548; PMCID: PMC3036477.

Kappel, S., Kandioler, D., Steininger, R. et al. (2006). Genetic detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. *Transplantation* 81 (1): 64–70.

Karanicolas, P.J. and Ko, Y.J. (2017). Hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the dawn of a new era? *Ann Surg Oncol* 24 (1): 6–7.

Kato, T., Yasui, K., Hirai, T. et al. (2003). Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. *Dis Colon Rectum* 46 (10 Suppl): S22–31.

Kavanagh, B.D., McGarry, R.C., and Timmerman, R.D. (2006). Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. *Semin Radiat Oncol* 16 (2): 77–84.

Kelly, H. and Goldberg, R.M. (2005). Systemic therapy for metastatic colorectal cancer: current options, current evidence. *J Clin Oncol* 23 (20): 4553–4560.

Kemeny, M.M., Adak, S., Gray, B. et al. (2002). Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy–an intergroup study. *J Clin Oncol* 20 (6): 1499–1505.

Kemeny, N., Gonen, M., Sullivan, D. et al. (2001). Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. *J Clin Oncol* 19 (10): 2687–2695.

Kemeny, N., Huang, Y., Cohen, A.M. et al. (1999). Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 341 (27): 2039–2048.

Kemeny, N.E. and Gonen, M. (2005). Hepatic arterial infusion after liver resection. *N Engl J Med* 352 (7): 734–735.

Kemeny, N.E., Jarnagin, W.R., Capanu, M. et al. (2011). Randomized phase II trial of adjuvant hepatic arterial infusion and systemic chemotherapy with or without bevacizumab in patients with resected hepatic metastases from colorectal cancer. *J Clin Oncol* 29 (7): 884–889.

Kemeny, N.E., Melendez, F.D., Capanu, M. et al. (2009). Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 27 (21): 3465–3471.

Kemeny, N.E., Niedzwiecki, D., and Hollis, D.R. (2003). Hepatic arterial infusion (HAI) versus systemic therapy for hepatic metastases from colorectal cancer; a CALGB randomized trial of efficacy, quality of life (QOL), cost effectiveness, and molecular markers. *Proc Am Soc Clin Oncol* 22: 252.

Kemeny, N.E., Niedzwiecki, D., Hollis, D.R. et al. (2006). Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol* 24 (9): 1395–1403.

Kennedy, A.S., Coldwell, D., Nutting, C. et al. (2006). Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys* 65 (2): 412–425.

Kim, A.Y., Unger, K., Wang, H., and Pishvaian, M.J. (2016). Incorporating Yttrium-90 trans-arterial radioembolization (TARE) in the treatment of metastatic pancreatic adenocarcioma: a single center experience. *BMC Cancer* 16 (1): 1–7.

Kim, C. (2018). Understanding the nuances of microwave ablation for more accurate post-treatment assessment. *Future Oncol* 14 (17): 1755–1764.

Kim, K.H., Yoon, Y.S., Yu, C.S. et al. (2011). Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. *J Korean Surg Soc* 81 (1): 25.

Kishi, Y., Abdalla, E.K., Chun, Y.S. et al. (2009). Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg* 250 (4): 540–548.

Kleiner, D.E., Brunt, E.M., Van Natta, M. et al. (2005). Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 41 (6): 1313–1321.

Köhne, C.-H., Poston, G., Folprecht, G. et al. (2016). FOLFIRI plus cetuximab in patients with liver-limited or non-liver-limited RAS wild-type metastatic colorectal cancer: a retrospective subgroup analysis of the CRYSTAL study. *Eur J Surg Oncol* 42 (10): 1540–1547.

Kubota, K., Makuuchi, M., Kusaka, K. et al. (1997). Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 26 (5): 1176–1181.

Kurilova, I., Pompa, V., Guerrero, R. et al. (2020). 90Y-Radioembolization After Failed Portal Vein Embolization for Colorectal Liver Metastases: a Case Report. *Cardiovasc Intervent Radiol* 43 (8): 1232–1236.

Lafaro, K.J., Stewart, C., Fong, A., and Fong, Y. (2020). Robotic liver resection. *Surg Clin N Am* 100 (2): 265–281.

Lahat, E., Eshkenazy, R., Zendel, A. et al. (2014). Complications after percutaneous ablation of liver tumors: a systematic review. *Hepatobiliary Surg Nutr* 3 (5): 317–323.

Lam, V.W.T., Laurence, J.M., Johnston, E. et al. (2013). A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases. *HPB* 15 (7): 483–491.

Le Roy, B., Perrey, A., Fontarensky, M. et al. (2017). Combined preoperative portal and hepatic vein embolization (biembolization) to improve liver regeneration before major liver resection: a preliminary report. *World J Surg* 41 (7): 1848–1856.

Lee, M.T., Kim, J.J., Dinniwell, R. et al. (2009). Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol* 27 (10): 1585–1591.

Leung, U., Simpson, A.L., Araujo, R.L.C. et al. (2014). Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure. *J Am Coll Surg* 219 (4): 620–630.

Levi, F.A., Boige, V., Hebbar, M. et al. and Association Internationale pour Recherche sur Temps Biologique et, C. (2016). Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV. *Ann Oncol* 27 (2): 267–274.

Lewandowski, R.J., Gabr, A., Abouchaleh, N. et al. (2018). Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. *Radiology* 287 (3): 1050–1058.

Lewandowski, R.J., Memon, K., Mulcahy, M.F. et al. (2014). Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging* 41 (10): 1861–1869.

Li, C., Gu, Y., Zhao, M. et al. (2014). Phase I trial of hepatic arterial infusion (HAI) of floxuridine with modified oxaliplatin, 5-fluorouracil and leucovorin (m-FOLFOX6) in Chinese patients with unresectable liver metastases from colorectal cancer. *Cancer Chemother Pharmacol* 74 (5): 1079–1087.

Liebl, M., Pedersoli, F., Zimmermann, M. et al. (2021). Induction of contralateral hepatic hypertrophy by unilobar yttrium-90 transarterial radioembolization versus portal vein embolization: an animal study. *J Vasc Interv Radiol* 32 (6): 836–842. e2.

Lievre, A., Bachet, J.-B., Le Corre, D. et al. (2006). KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 66 (8): 3992–3995.

Lim, L., Gibbs, P., Yip, D. et al. (2005). A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. *BMC Cancer* 5: 132.

Lin, Y.-M., Paolucci, I., Brock, K.K., and Odisio, B.C. (2021). Image-guided ablation for colorectal liver metastasis: principles, current evidence, and the path forward. *Cancers* 13 (16): 3926.

Linecker, M., Stavrou, G.A., Oldhafer, K.J. et al. (2016). The ALPPS risk score. *Ann Surg* 264 (5): 763–771.

Littrup, P.J., Aoun, H.D., Adam, B. et al. (2016). Percutaneous cryoablation of hepatic tumors: long-term experience of a large U.S. series. *Abdom Radiol* 41 (4): 767–780.

Lordan, J., Karanjia, N., Quiney, N. et al. (2009). A 10-year study of outcome following hepatic resection for colorectal liver metastases–the effect of evaluation in a multidisciplinary team setting. *Eur J Surg Oncol* 35 (3): 302–306.

Luo, M., Chen, S.L., Chen, J. et al. (2020). Resection vs. ablation for lesions characterized as resectable-ablative within the colorectal liver oligometastases criteria: a propensity score matching from retrospective study. *PeerJ* 8: e8398.

Luz, J.H.M., Veloso Gomes, F., Costa, N.V. et al. (2021). BestFLR Trial: liver regeneration at CT before major hepatectomies for liver cancer—A randomized controlled trial comparing portal vein embolization with N-butyl-cyanoacrylate plus iodized oil versus polyvinyl alcohol particles plus coils. *Radiology* 299 (3): 715–724.

Madoff, D.C., Abdalla, E.K., and Vauthey, J.-N. (2005). Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. *J Vasc Interv Radiol* 16 (6): 779–790.

Maeda, T., Hasebe, Y., Hanawa, S. et al. (1992). Trial of percutaneous hepatic cryo therapy: preliminary report. *Nihon Geka Gakkai Zasshi* 93 (6): 666-666.

Makowiec, F., Bronsert, P., Klock, A. et al. (2018). Prognostic influence of hepatic margin after resection of colorectal liver metastasis: role of modern preoperative chemotherapy. *Int J Colorectal Dis* 33 (1): 71–78.

Malhotra, A., Liu, D.M., and Talenfeld, A.D. (2019). Radiation segmentectomy and radiation lobectomy: a practical review of techniques. *Tech Vasc Interv Radiol* 22 (2): 49–57.

Maor, E., Ivorra, A., Leor, J., and Rubinsky, B. (2007). The effect of irreversible electroporation on blood vessels. *Technol Cancer Res Treat* 6 (4): 307–312.

Margonis, G.A., Buettner, S., Andreatos, N. et al. (2019). Prognostic factors change over time after hepatectomy for colorectal liver metastases: a multi-institutional, international analysis of 1099 patients. *Ann Surg* 269 (6): 1129–1137.

Margonis, G.A., Sasaki, K., Kim, Y. et al. (2016). Tumor biology rather than surgical technique dictates prognosis in colorectal cancer liver metastases. *J Gastrointest Surg* 20 (11): 1821–1829.

Margonis, G.A., Spolverato, G., Kim, Y. et al. (2015a). Intraoperative surgical margin re-resection for colorectal liver metastasis: is it worth the effort? *J Gastrointest Surg* 19 (4): 699–707.

Margonis, G.A., Spolverato, G., Kim, Y. et al. (2015b). Effect of KRAS mutation on long-term outcomes of patients undergoing hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 22 (13): 4158–4165.

Mastrolonardo, E., Jia, J., Eng, B. et al. (2020). Comparison of percutaneous ethanol injection and radiofrequency ablation for the treatment of hepatocellular carcinoma. *Am J Intervent Radiol* 4: 16.

Mayer, R.J., Van Cutsem, E., Falcone, A. et al. (2015). Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 372 (20): 1909–1919.

McPartlin, A., Swaminath, A., Wang, R. et al. (2017). Long-term outcomes of phase 1 and 2 studies of SBRT for hepatic colorectal metastases. *Int J Radiat Oncol Biol Phys* 99 (2): 388–395.

Meijerink, M.R., Ruarus, A.H., Vroomen, L. et al. (2021). Irreversible electroporation to treat unresectable colorectal liver metastases (COLDFIRE-2): a phase II, two-center, single-arm clinical trial. *Radiology* 299 (2): 470–480.

Melstrom, L.G., Warner, S.G., Woo, Y. et al. (2018). Selecting incision-dominant cases for robotic liver resection: towards outpatient hepatectomy with rapid recovery. *Hepatobiliary Surg Nutr* 7 (2): 77–84.

Meric-Bernstam, F., Hainsworth, J., Bose, R. et al. (2021 May 20). MyPathway HER2 basket study: pertuzumab (P) + trastuzumab (H) treatment of a large, tissue-agnostic cohort of patients with HER2-positive advanced solid tumor s. *J Clin Oncol* 39 (15_suppl): doi: 10.1200/JCO.2021.39.15_suppl.3004.

Michal, K., Sau, M., Tamara, G.M.H., and Long, J.R. (2020). A better route to ALPPS: minimally invasive vs open ALPPS. *Surg Endosc* 34 (6): 2379–2389.

Miften, M., Vinogradskiy, Y., Moiseenko, V. et al. (2021). Radiation dose-volume effects for liver SBRT. *Int J Radiat Oncol Biol Phys* 110 (1): 196–205.

Miller, L., Leor, J., and Rubinsky, B. (2005). Cancer cells ablation with irreversible electroporation. *Technol Cancer Res Treat* 4 (6): 699–705.

Minagawa, M., Makuuchi, M., Torzilli, G. et al. (2000). Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. *Ann Surg* 231 (4): 487–499.

Mohamad, I., Barry, A., Dawson, L., and Hosni, A. (2022). Stereotactic body radiation therapy for colorectal liver metastases. *Int J Hyperth* 39 (1): 611–619.

Mor, E., Al-Kurd, A., Ben Yaacov, A. et al. (2019). Surgical outcomes of two-stage hepatectomy for colorectal liver metastasis: comparison to a benchmark procedure. *Hepatobiliary Surg Nutr* 8 (1): 29–36.

Moris, D., Ronnekleiv-Kelly, S., Rahnemai-Azar, A.A. et al. (2017). Parenchymal-sparing versus anatomic liver resection for colorectal liver metastases: a systematic review. *J Gastrointest Surg* 21 (6): 1076–1085.

Mulcahy, M.F., Mahvash, A., Pracht, M. et al. (2021a). Radioembolization with chemotherapy for colorectal liver metastases: a randomized, open-label, international, multicenter, phase III trial. *J Clin Oncol* 39 (35): 3897–3907.

Mulcahy, M.F., Salem, R., Mahvash, A. et al. (2021b). LBA21 Radioembolization with chemotherapy for colorectal liver metastases: a randomized, open-label, international, multicenter, phase III trial (EPOCH study). *Ann Oncol* 32: S1295.

Mulier, S., Ruers, T., Jamart, J. et al. (2008). Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Dig Surg* 25 (6): 445–460.

Muratore, A., Polastri, R., Bouzari, H. et al. (2001). Repeat hepatectomy for colorectal liver metastases: a worthwhile operation? *J Surg Oncol* 76 (2): 127–132.

Mutsaerts, E.L., van Ruth, S., Zoetmulder, F.A. et al. (2005). Prognostic factors and evaluation of surgical management of hepatic metastases from colorectal origin: a 10-year single-institute experience. *J Gastrointest Surg* 9 (2): 178–186.

Narayanan, G. (2015). Irreversible electroporation. *Semin Intervent Radiol* 32 (04): 349–355.

Neal, C.P., Nana, G.R., Jones, M. et al. (2017). Repeat hepatectomy is independently associated with favorable long-term outcome in patients with colorectal liver metastases. *Cancer Med* 6 (2): 331–338.

Niekamp, A.S., Huang, S.Y., Mahvash, A. et al. (2020). Hepatic vein embolization after portal vein embolization to induce additional liver hypertrophy in patients with metastatic colorectal carcinoma. *Eur Radiol* 30 (7): 3862–3868.

Niekel, M.C., Bipat, S., and Stoker, J. (2010). Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 257 (3): 674–684.

Nielsen, K., Van Tilborg, A.A.J.M., Meijerink, M.R. et al. (2013). Incidence and treatment of local site recurrences following RFA of colorectal liver metastases. *World J Surg* 37 (6): 1340–1347.

Nordlinger, B., Guiguet, M., Vaillant, J.C. et al. (1996). Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 77 (7): 1254–1262.

Nordlinger, B., Quilichini, M.A., Parc, R. et al. (1987). Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. *Ann Surg* 205 (3): 256–263.

Nordlinger, B., Sorbye, H., Glimelius, B. et al. (2008). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 371 (9617): 1007–1016.

Nordlinger, B., Sorbye, H., Glimelius, B. et al. (2013). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 14 (12): 1208–1215.

Northover, J.M. and Terblanche, J. (1979). A new look at the arterial supply of the bile duct in man and its surgical implications. *Br J Surg* 66 (6): 379–384.

Okuno, M., Kawaguchi, Y., De Bellis, M. et al. (2021). A new sequential treatment strategy for multiple colorectal liver metastases: planned incomplete resection and postoperative completion ablation for intentionally-untreated tumors under guidance of cross-sectional imaging. *Eur J Surg Oncol* 47 (2): 311–316.

Oxley, E.M. and Ellis, H. (1969). Prognosis of carcinoma of the large bowel in the presence of liver metastases. *Br J Surg* 56 (2): 149–152.

Palma, D.A., Olson, R., Harrow, S. et al. (2020). Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol* 38 (25): 2830–2838.

Pearson, A.S., Izzo, F., Fleming, R.Y. et al. (1999). Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg* 178 (6): 592–599.

Penn, I. (1991). Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery* 110 (4): 726–734; discussion 734-5.

Petrowsky, H., Gonen, M., Jarnagin, W. et al. (2002). Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann Surg* 235 (6): 863–871.

Petrowsky, H., Linecker, M., Raptis, D.A. et al. (2020). First long-term oncologic results of the ALPPS procedure in a large cohort of patients with colorectal liver metastases. *Ann Surg* 272 (5): 793–800.

Pfeiffer, P., Yilmaz, M., Möller, S. et al. (2020). TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. *Lancet Oncol* 21 (3): 412–420.

Polivka, J., Windrichova, J., Pesta, M. et al. (2020). The level of preoperative plasma KRAS mutations and CEA predict survival of patients undergoing surgery for colorectal cancer liver metastases. *Cancers* 12 (9): 2434.

Puijk, R.S., Ruarus, A.H., Vroomen, L.G.P.H. et al. (2018). Colorectal liver metastases: surgery versus thermal ablation (COLLISION) – a phase III single-blind prospective randomized controlled trial. *BMC Cancer* 18: 1.

Raoof, M., Haye, S., Ituarte, P.H.G., and Fong, Y. (2019). Liver resection improves survival in colorectal cancer patients: causal-effects from population-level instrumental variable analysis. *Ann Surg* 270 (4): 692–700.

Riaz, A., Gates, V.L., Atassi, B. et al. (2011). Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys* 79 (1): 163–171.

Ribero, D., Abdalla, E., Madoff, D. et al. (2007a). Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *J Br Surg* 94 (11): 1386–1394.

Ribero, D., Chun, Y.S., and Vauthey J.N. (2008 June). Standardized liver volumetry for portal vein embolization. *Semin Intervent Radiol* 25 (2): 104–109. doi: 10.1055/s-2008-1076681. PMID: 21326551; PMCID: PMC3036478.

Ribero, D., Wang, H., Donadon, M. et al. (2007b). Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer* 110 (12): 2761–2767.

Ridouani, F., Soliman, M.M., England, R.W. et al. (2021). Relationship of radiation dose to efficacy of radioembolization of liver metastasis from breast cancer. *Eur J Radiol* 136: 109539.

Rosen, C.B., Nagorney, D.M., Taswell, H.F. et al. (1992). Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. *Ann Surg* 216 (4): 493–504; discussion 504-5.

Rougier, P., Van Cutsem, E., Bajetta, E. et al. (1998). Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 352 (9138): 1407–1412.

Rubbia-Brandt, L., Lauwers, G.Y., Wang, H. et al. (2010). Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology* 56 (4): 430–439.

Ruers, T., Van Coevorden, F., Punt, C.J.A. et al. (2017). Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 109: 9.

Rusthoven, K.E., Kavanagh, B.D., Cardenes, H. et al. (2009). Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 27 (10): 1572–1578.

Sadot, E., Koerkamp, B.G., Leal, J.N. et al. (2015). Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer. *Ann Surg* 262 (3): 476–485.

Salem, R., Padia, S.A., Lam, M. et al. (2019). Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging* 46 (8): 1695–1704.

Saltz, L.B., Clarke, S., Diaz-Rubio, E. et al. (2008). Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 26 (12): 2013–2019.

Saltz, L.B., Cox, J.V., Blanke, C. et al. (2000). Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 343 (13): 905–914.

Sandström, P., Røsok, B.I., Sparrelid, E. et al. (2018a). ALPPS improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a Scandinavian multicenter randomized controlled trial (LIGRO trial). *Ann Surg* 267 (5): 833.

Sandström, P., Røsok, B.I., Sparrelid, E. et al. (2018b). ALPPS improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a Scandinavian multicenter randomized controlled trial (LIGRO Trial). *Ann Surg* 267 (5): 833–840.

Sartore-Bianchi, A., Trusolino, L., Martino, C. et al. (2016). Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 17 (6): 738–746.

Sasaki, K., Morioka, D., Conci, S. et al. (2018). The tumor burden score: a new "metro-ticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. *Ann Surg* 267 (1): 132–141.

Scheele, J., Stang, R., Altendorf-Hofmann, A., and Paul, M. (1995a). Resection of colorectal liver metastases. *World J Surg* 19 (1): 59–71.

Scheele, J., Stang, R., tendorf-Hofmann, A., and Paul, M. (1995b). Resection of colorectal liver metastases. *World J Surg* 19 (1): 59–71.

Scheele, J., Stangl, R., and Altendorf-Hofmann, A. (1990). Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 77 (11): 1241–1246.

Scheele, J., Stangl, R., Altendorf-Hofmann, A., and Gall, F.P. (1991). Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery* 110 (1): 13–29.

Scheffer, H.J., Nielsen, K., Van Tilborg, A.A.J.M. et al. (2014). Ablation of colorectal liver metastases by irreversible electroporation: results of the COLDFIRE-I ablate-and-resect study. *Eur Radiol* 24 (10): 2467–2475.

Schefter, T.E., Kavanagh, B.D., Timmerman, R.D. et al. (2005). A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int J Radiat Oncol Biol Phys* 62 (5): 1371–1378.

Schlag, P., Hohenberger, P., and Herfarth, C. (1990). Resection of liver metastases in colorectal cancer–competitive analysis of treatment results in synchronous versus metachronous metastases. *Eur J Surg Oncol* 16 (4): 360–365.

Schnitzbauer, A.A., Lang, S.A., Goessmann, H. et al. (2012). Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 255 (3): 405–414.

Scorsetti, M., Comito, T., Clerici, E. et al. (2018). Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. *Radiat Oncol* 13 (1): 234.

Seifert, J.K. and Junginger, T. (2004). Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature. *Technol Cancer Res Treat* 3 (2): 151–163.

Seifert, J.K. and Morris, D.L. (1999). World survey on the complications of hepatic and prostate cryotherapy. *World J Surg* 23 (2): 109–114.

Shady, W., Petre, E.N., Do, K.G. et al. (2018). Percutaneous microwave versus radiofrequency ablation of colorectal liver metastases: ablation with clear margins (A0) provides the best local tumor control. *J Vasc Interv Radiol* 29 (2): 268–275.e1.

Shaw, I.M., Rees, M., Welsh, F.K. et al. (2006). Repeat hepatic resection for recurrent colorectal liver metastases is associated with favourable long-term survival. *Br J Surg* 93 (4): 457–464.

Shindoh, J., Truty, M.J., Aloia, T.A. et al. (2013a). Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg* 216 (2): 201–209.

Shindoh, J., Tzeng, C.-W.D., Aloia, T.A. et al. (2013b). Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol* 20 (8): 2493–2500.

Shindoh, J., Tzeng, C.-W.D., Aloia, T.A. et al. (2013c). Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol* 20 (8): 2493–2500.

Simmonds, P.C., Primrose, J.N., Colquitt, J.L. et al. (2006). Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 94 (7): 982–999.

Simoneau, E., Hassanain, M., Shaheen, M. et al. (2015). Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases. *J Br Surg* 102 (10): 1240–1249.

Sofocleous, C.T., Petre, E.N., Gonen, M. et al. (2011). CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. *J Vasc Interv Radiol* 22 (6): 755–761.

Soliman, H., Ringash, J., Jiang, H. et al. (2013). Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. *J Clin Oncol* 31 (31): 3980–3986.

Sorich, M.J., Wiese, M.D., Rowland, A. et al. (2015). Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Ann Oncol* 26 (1): 13–21.

Soubrane, O., Brouquet, A., Zalinski, S. et al. (2010). Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. *Ann Surg* 251 (3): 454–460.

Stangl, R., Altendorf-Hofmann, A., Charnley, R.M., and Scheele, J. (1994). Factors influencing the natural history of colorectal liver metastases. *Lancet* 343 (8910): 1405–1410.

Stephenson, K.R., Steinberg, S.M., Hughes, K.S. et al. (1988). Perioperative blood transfusions are associated with decreased time to recurrence and decreased survival after resection of colorectal liver metastases. *Ann Surg* 208 (6): 679–687.

Stewart, C. and Fong, Y. (2020). Clinical scoring systems for colorectal cancer liver metastases. In: *Colorectal Cancer Liver Metastases* (ed. M.M. Correia, M.A. Choti, F.G. Rocha and G. Wakabayashi), 95–111. Springer International Publishing.

Stewart, C. and Fong, Y. (2021). Robotic liver surgery—advantages and limitations. *Eur Surg* 53 (4): 149–157.

Stewart, C., Wong, P., Warner, S. et al. (2021 May). Robotic minor hepatectomy: optimizing outcomes and cost of care. *HPB (Oxford)* 23 (5): 700–706. doi: 10.1016/j.hpb.2020.09.005. Epub 2020 Sep 25. PMID: 32988754.

Stewart, C.L., Warner, S., Ito, K. et al. (2018). Cytoreduction for colorectal metastases: liver, lung, peritoneum, lymph nodes, bone, brain. When does it palliate, prolong survival, and potentially cure? *Curr Probl Surg* 55 (9): 330–379.

Strasberg, S.M., Dehdashti, F., Siegel, B.A. et al. (2001). Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg* 233 (3): 293–299.

Suzuki, S., Nakamura, S., Ochiai, H. et al. (1997). Surgical management of recurrence after resection of colorectal liver metastases. *J Hepatobiliary Pancreat Surg* 4 (1): 103–112.

Suzuki, S., Sakaguchi, T., Yokoi, Y. et al. (2001). Impact of repeat hepatectomy on recurrent colorectal liver metastases. *Surgery* 129 (4): 421–428.

Swierz, M.J., Storman, D., Riemsma, R.P. et al. (2020). Percutaneous ethanol injection for liver metastases. *Cochrane Database Syst Rev* (2020): 2.

Takamoto, T., Hashimoto, T., Miyata, A. et al. (2020). Repeat hepatectomy after major hepatectomy for colorectal liver metastases. *J Gastrointest Surg* 24 (2): 380–387.

Tandon, R.N., Bunnell, I.L., and Cooper, R.G. (1973). The treatment of metastatic carcinoma of the liver by the percutaneous selective hepatic artery infusion of 5-fluorouracil. *Surgery* 73 (1): 118–121.

Tang, W., Ren, L., Liu, T. et al. (2020). Bevacizumab plus mFOLFOX6 versus mFOLFOX6 alone as first-line treatment for RAS mutant unresectable colorectal liver-limited metastases: the BECOME randomized controlled trial. *J Clin Oncol* 38 (27): 3175–3184.

Teo, J.-Y. and Goh, B.K. (2015). Contra-lateral liver lobe hypertrophy after unilobar Y90 radioembolization: an alternative to portal vein embolization? *WJG, World J Gastroenterol* 21 (11): 3170.

Thomson, K.R., Cheung, W., Ellis, S.J. et al. (2011). Investigation of the safety of irreversible electroporation in humans. *J Vasc Interv Radiol* 22 (5): 611–621.

Thornblade, L.W., Warner, S., Melstrom, L. et al. (2020). Association of race/ethnicity with overall survival among patients with colorectal liver metastasis. *JAMA Network Open* 3 (9): e2016019.

Tinguely, P., Dal, G., Bottai, M. et al. (2020). Microwave ablation versus resection for colorectal cancer liver metastases – a propensity score analysis from a population-based nationwide registry. *Eur J Surg Oncol* 46 (3): 476–485.

Tol, J., Koopman, M., Cats, A. et al. (2009). Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 360 (6): 563–572.

Tomasello, G., Petrelli, F., Ghidini, M. et al. (2017). FOLFOXIRI plus bevacizumab as conversion therapy for patients with initially unresectable metastatic colorectal cancer: a systematic review and pooled analysis. *JAMA Oncol* 3 (7): e170278.

Torres, O.J.M., Fernandes, E.D.S.M., Oliveira, C.V.C. et al. (2013). Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): the Brazilian experience. *ABCD Arquivos Brasileiros de Cirurgia Digestiva (São Paulo)* 26: 40–43.

Tosi, F., Magni, E., Amatu, A. et al. (2017). Effect of KRAS and BRAF mutations on survival of metastatic colorectal cancer after liver resection: a systematic review and meta-analysis. *Clinical Colorectal Cancer* 16 (3): e153–e163.

Tournigand, C., Andre, T., Achille, E. et al. (2004). FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 22 (2): 229–237.

Truant, S., Scatton, O., Dokmak, S. et al. (2015). Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): impact of the inter-stages course on morbi-mortality and implications for management. *Eur J Surg Oncol* 41 (5): 674–682.

Tsilimigras, D.I., Ntanasis-Stathopoulos, I., Bagante, F. et al. (2018). Clinical significance and prognostic relevance of KRAS, BRAF, PI3K and TP53 genetic mutation analysis for resectable and unresectable colorectal liver metastases: a systematic review of the current evidence. *Surg Oncol* 27 (2): 280–288.

Van Cutsem, E., Cervantes, A., Adam, R. et al. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27 (8): 1386–1422.

Van Cutsem, E., Kohne, C.H., Hitre, E. et al. (2009). Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360 (14): 1408–1417.

Van Der Stok, E.P., Verhoef, C., and Grunhagen, D.J. (2016). Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial. *J Clin Oncol* 34 (4_suppl): TPS790–TPS790.

Van Hazel, G.A., Heinemann, V., Sharma, N.K., and Peeters, M. (2016). SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol New York* 34 (15): 1723–1731.

Vauthey, J.-N., Abdalla, E.K., Doherty, D.A. et al. (2002). Body surface area and body weight predict total liver volume in Western adults. *Liver Transplant* 8 (3): 233–240.

Vauthey, J.-N. and Mizuno, T. (2017). Portal vein embolization: tailoring, optimizing, and quantifying an invaluable procedure in hepatic surgery. *Ann Surg Oncol* 24 (6): 1456–1458.

Vauthey, J.-N., Pawlik, T.M., Ribero, D. et al. (2006). Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 24 (13): 2065–2072.

Venook, A.P., Niedzwiecki, D., Innocenti, F. et al. (2016). Impact of primary tumor location on overall survival and progression-free survival in patients with metastatic colorectal cancer: analysis of CALGB/SWOG 80405. *J Clin Oncol* 3504.

Viganò, L., Rubbia-Brandt, L., De Rosa, G. et al. (2015). Nodular regenerative hyperplasia in patients undergoing liver resection for colorectal metastases after chemotherapy: risk factors, preoperative assessment and clinical impact. *Ann Surg Oncol* 22 (13): 4149–4157.

Volchok, H.L. and Kulp, J.L. (1955). 'Half-life of yttrium-90'. *Phys Rev* 97 (1): 102.

Vouche, M., Lewandowski, R.J., Atassi, R. et al. (2013). Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J Hepatol* 59 (5): 1029–1036.

Wagner, J.S., Adson, M.A., Van Heerden, J.A. et al. (1984). The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. *Ann Surg* 199 (5): 502–508.

Wasan, H.S., Gibbs, P., Sharma, N.K. et al. (2017). First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 18 (9): 1159–1171.

Wei, A.C., Greig, P.D., Grant, D. et al. (2006). Survival after hepatic resection for colorectal metastases: a 10-year experience. *Ann Surg Oncol* 13 (5): 668–676.

Wilson, S.M. and Adson, M.A. (1976). Surgical treatment of hepatic metastases from colorectal cancers. *Arch Surg* 111 (4): 330–334.

Wiseman, J.T., Guzman-Pruneda, F., Xourafas, D. et al. (2019). Impact of neoadjuvant chemotherapy on the postoperative outcomes of patients undergoing liver resection for colorectal liver metastases: a population-based propensity-matched analysis. *J Am Coll Surg* 229 (1): 69–77.e2.

Wood, C.B., Gillis, C.R., and Blumgart, L.H. (1976). A retrospective study of the natural history of patients with liver metastases from colorectal cancer. *Clin Oncol* 2 (3): 285–288.

Wu, C. (2018). Systemic therapy for colon cancer. *Surg Oncol Clin N Am* 27 (2): 235–242.

Yamamoto, J., Kosuge, T., Shimada, K. et al. (1999). Repeat liver resection for recurrent colorectal liver metastases. *Am J Surg* 178 (4): 275–281.

Younes, R.N., Rogatko, A., and Brennan, M.F. (1991). The influence of intraoperative hypotension and perioperative blood transfusion on disease-free survival in patients with complete resection of colorectal liver metastases. *Ann Surg* 214 (2): 107–113.

Yu, J., Liang, P., Yu, X.L. et al. (2012). Needle track seeding after percutaneous microwave ablation of malignant liver tumors under ultrasound guidance: analysis of 14-year experience with 1462 patients at a single center. *Eur J Radiol* 81 (10): 2495–2499.

Zech, C.J., Herrmann, K.A., Reiser, M.F., and Schoenberg, S.O. (2007). MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent Gd-EOB-DTPA. *Magn Reson Med Sci* 6 (1): 43–52.

Zhang, Q., Peng, J., Ye, M. et al. (2020). KRAS mutation predicted more mirometastases and closer resection margins in patients with colorectal cancer liver metastases. *Ann Surg Oncol* 27 (4): 1164–1173.

Zhao, J., Van Mierlo, K.M.C., Gómez-Ramírez, J. et al. (2017). Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. *Br J Surg* 104 (8): 990–1002.

Zhao, Q., Cheng, Z., Han, Z. et al. (2021). Percutaneous microwave ablation versus open surgical resection for colorectal cancer liver metastasis. *Frontiers in Oncology* 11.

Zimmermann, M., Pedersoli, F., Schulze-Hagen, M. et al. (2020). Salvage RFA in patients with intrahepatic recurrence after major hepatic surgery for colorectal cancer liver metastases: mid-term outcome. *Eur Radiol* 30 (2): 1221–1227.

Zorzi, D., Laurent, A., Pawlik, T. et al. (2007). Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *J Br Surg* 94 (3): 274–286.

Zorzi, D., Mullen, J.T., Abdalla, E.K. et al. (2006). Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. *J Gastrointest Surg* 10 (1): 86–94.

20 Management of Primary Pancreatic Cancer

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Introduction

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Globally, primary pancreatic cancer is the seventh most common cause of cancer deaths (Bray et al. 2018). In Australia this has now become the third commonest cause of cancer deaths (AIHW 2021), and it is projected to move to second most common cause of cancer deaths by 2030 (Rahib et al. 2014; Siegel et al. 2022). The most common subtype is pancreatic ductal adenocarcinoma (PDAC) which comprises 85% of all pancreatic carcinomas. The five-year overall survival rate for PDAC is 11% for all stages combined and has improved modestly from 6.5% in 2007–2019, attributed to both earlier diagnosis and new treatments (AIHW 2021). Survival correlates with stage and surgical resectability. Surgical resection is considered feasible if systemic dissemination is absent, and local invasion of adjacent structures such as major vessels is not evident; discussed further in the **Surgery** section of this chapter. Only 20% of patients have resectable disease at diagnosis (Butturini et al. 2008), and approximately 15% can undergo complete surgical resection (Burmeister et al. 2015). The majority of patients have metastatic or locally advanced disease at diagnosis (80–85%) with a poor outcome of 3% overall survival at five years (Siegel et al. 2022). A major contributing factor to the poor prognosis is chemoresistance and the negative role of tumor stroma which is further discussed in the **Biology** section.

Biology

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PDAC originates from ductal epithelial cells in the pancreas and evolves from pre-malignant lesions (pancreatic intraepithelial neoplasia, PanIN) (Hidalgo 2010). Genomic and transcriptomic data have identified distinct subtypes of PDAC that correlate with varying degrees of patient outcome and chemotherapy response (Bailey et al. 2016; Collisson et al. 2011; Moffitt et al. 2015; Waddell et al. 2015). However, actionable molecular targets in PDAC patients are infrequent at 20–30% (Bailey et al. 2016; Waddell et al. 2015), and overlaid with access and clinical barriers – with two key studies showing that only 2–3% of PDAC patients who were referred to a precision medicine program received personalized targeted therapy (Ding et al. 2021; Pishvaian et al. 2020). The bigger opportunity for precision medicine in PDAC may instead lie in the microenvironment of PDAC (Kokkinos et al. 2021a).

Early in PDAC development, a marked desmoplastic reaction occupies up to 90% of the PDAC tumor and is composed of extracellular matrix (ECM) and stromal cells, mainly consisting of cancer-associated fibroblasts (CAFs) (Erkan et al. 2012; Li et al. 2010; Phillips 2012). CAFs produce the dense fibrosis in PDAC which compresses tumor vasculature and increases intratumoral fluid pressure, creating a physical barrier to drug delivery and immune cell penetration (Diop-Frimpong et al. 2011; Olive et al. 2009b; Provenzano et al. 2012). Importantly, certain stromal features in PDAC, including high cross-linked collagen or hyaluronan content for example, correlate with poor patient outcome (Cheng et al. 2013; Erkan et al. 2008; Miller et al. 2015; Whatcott et al. 2015). High levels of hypoxia, nutrient deprivation, and oxidative stress created by the tumor microenvironment (Kamphorst et al. 2015; Martinez-Useros et al. 2017; Pan et al. 2016; Tao et al. 2021) also drive the selection of aggressive and

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heterogeneous clones of PDAC and CAF cells with a more chemoresistant and metastatic phenotype (Chaika et al. 2012; Cheng et al. 2014; Qin et al. 2020; Shukla et al. 2017; Tréhoux et al. 2015).

Additionally, CAFs directly exert pro-tumorigenic effects on surrounding PDAC cells through the release of cytokines, growth factors, and nutrients, and the formation of an immune-suppressive landscape (Huber et al. 2020; Karamitopoulou 2019). For example, a recent study showed that PDAC CAFs are highly reliant on the cystine transporter SLC7A11 and dual-cell therapeutic targeting of SLC7A11 in both PDAC cells and CAFs reduced fibrosis and tumor progression *in vivo* (Sharbeen et al. 2021). Furthermore, CAFs are capable of promoting metastasis of PDAC cells (Hwang et al. 2012; Pan et al. 2021; Vonlaufen et al. 2008; Xu et al. 2010). This process can be stimulated by CAF secretions such as TGF-β (Ligorio et al. 2019). Additionally, evidence has shown that CAFs are capable of metastasizing together with PDAC cells to promote the formation of a pro-metastatic niche in distant organ sites (Xu et al. 2010).

The above evidence suggests the therapeutic potential of targeting pro-tumor functions of CAFs and the stroma for PDAC treatment. However, clinical trials targeting the PDAC stroma have failed to show survival advantage to PDAC patients. The sonic hedgehog inhibitor vismodegib, which showed promise in preclinical studies (Olive et al. 2009a), showed no treatment benefit in phase I and II clinical trials (Catenacci et al. 2015; Kim et al. 2014). An enzymatic approach to degrade the PDAC stroma using the drug PEGPH20 showed encouraging preclinical activity (Provenzano et al. 2012), but a phase III trial in metastatic PDAC patients showed no survival benefit (Van Cutsem et al. 2020). These failed clinical trials show that targeting the stroma alone as a "one-size-fits-all" approach is unlikely to be effective. Recent research has shifted towards an approach of understanding the inter-patient and intra-patient cellular heterogeneity of the PDAC stroma to design more personalized therapeutic strategies.

Recent advances in single cell transcriptomics have identified subtypes of CAFs with proposed distinct functions within the PDAC microenvironment (Elyada et al. 2019; Öhlund et al. 2017). This is further complicated by the observation that stromal transcriptomic signatures within the spatial architecture of PDAC show distinct associations with patient outcomes (Ligorio et al. 2019); although the functional role of these stromal signatures need to be validated to allow for therapeutic exploitation.

To facilitate translation of therapeutics that target the PDAC stroma, preclinical models need to accurately mimic the complexity and heterogeneity of human PDAC. The PDAC tumor explant model, which maintains the viability, 3D tumor and stromal architecture, and genetic drivers of surgical patient PDAC tissue for 12 days, carries potential to guide the translation of stromal targeting strategies (Kokkinos et al. 2021b; Sharbeen et al. 2021). These explants can be utilized in a precision medicine setting based on stromal and/or tumor signatures of each patient as a functional tool to inform patient treatment in real-time (Kokkinos et al. 2021a).

To maximize the translation of recent scientific advances, an active collaboration is required between researchers and clinicians so that researchers gain a clinically relevant perspective, while clinicians can facilitate the clinical translation of promising new therapeutic strategies.

Areas for Further Research

- It remains unknown how the high degree of transcriptional and spatial heterogeneity of the PDAC stroma influences patient response to chemotherapy and whether distinct CAF subtypes can be therapeutically exploited.
- Pre-clinical models that accurately mimic the complexity and heterogeneity of human PDAC are needed to guide the translation of novel therapeutic strategies that target tumor and stromal cells.
- Need for understanding the basis of response and failure to targeted tumor and stromal therapies, and development of novel therapeutic strategies for future evaluation. This can involve embedding deep correlative science on pre- and post-treatment specimens in mice and humans.

Incorporating Translational Scientists in the Clinic to Maximize Translation

John Kokkinos, George Sharbeen & Phoebe A. Phillips

The inclusion of translational research teams in cancer MDT meetings can bridge the gap between research lab and clinic. These meetings provide opportunities for researchers to follow the whole cycle of patient management and appreciate the clinical challenges faced by PDAC patients. Key issues we now appreciate are that patient treatment selection is often based on performance status and comorbidity profile rather than tumor biology alone – reinforcing the need for functional precision medicine tools to guide treatment selection. Furthermore, disease progression is often rapid, so precision medicine tools must have fast turnaround times to be clinically meaningful. Another unmet clinical challenge is that most patients present with metastatic disease yet most research involves cell lines or tissue samples obtained from surgically resectable disease, which represent a minority of PDAC patients with better prognosis. Future collaborative research should focus on obtaining metastatic tissue samples for research purposes and integrating scientists in trial design to allow integrated scientific evaluation of clinical trial samples pre- and post-treatment to understand the biological basis behind success or failure of new therapeutics as well as basic scientific discoveries (Figure 1).

To allow for seamless integration of translational scientists into cancer MDT meetings, educational programs should be available for researchers to upskill their clinical expertise to be able to follow the fast-paced nature of an MDT meeting. This will enable scientists to contribute to MDT meetings – while they may not be able to directly influence patient management, they can educate the MDT on the latest advancements in research and how the present clinical challenge can be potentially solved by future developments in the field.

Multidisciplinary Team

Omali Pitiyarachchi & David Goldstein

Multidisciplinary care has become the gold standard in the management of patients with pancreatic cancer (Maharaj et al. 2021). The purpose of the MDT includes establishing the diagnosis by evaluating the patient's history, tumor pathology, biomarkers, and imaging. It also encompasses staging, a decision about tumor resectability, and overall management plan. In cases where upfront resection is not possible, or metastatic disease is present, then a discussion regarding optimum radiation and/or systemic therapy is recommended. There may also be cases where the best recommendation for the patient is for no intervention.

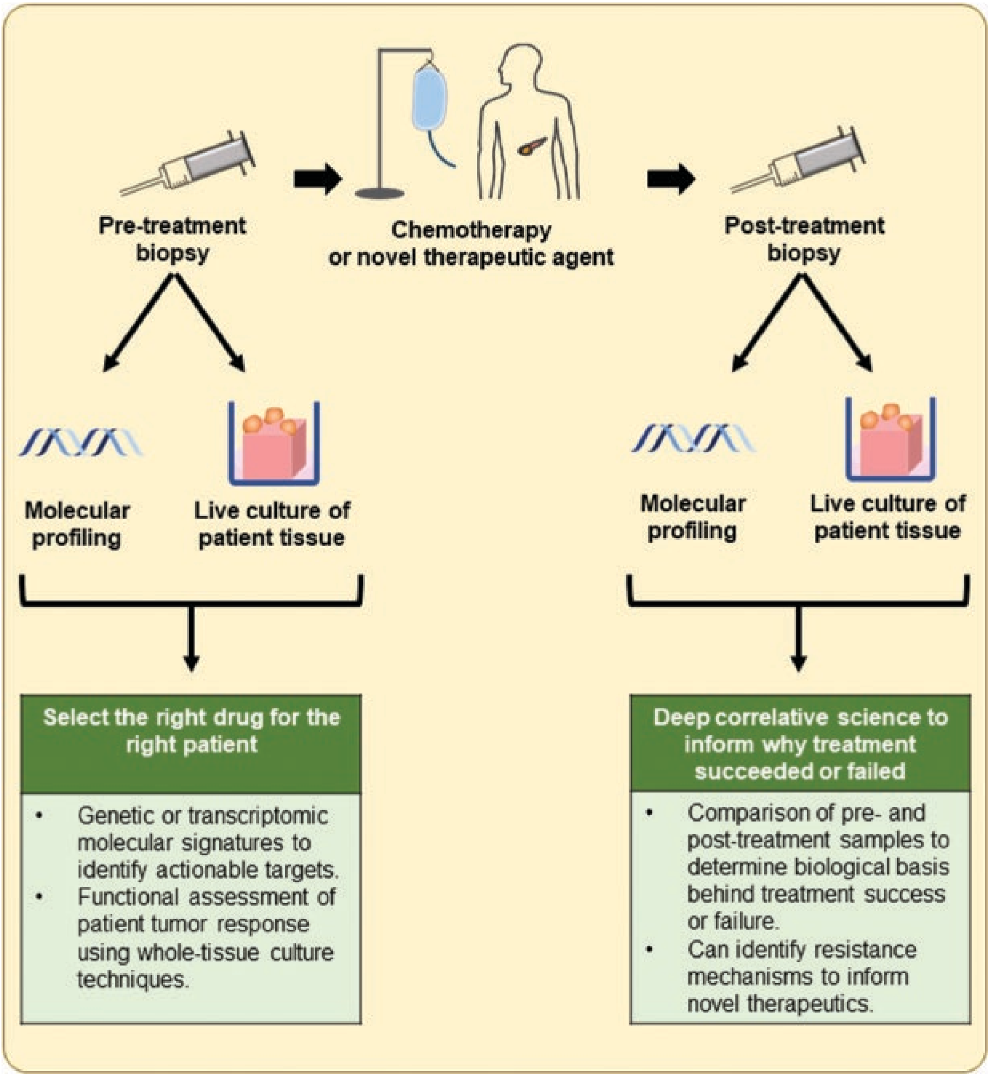

Pre-treatment biopsy
Chemotherapy or novel therapeutic agent
Post-treatment biopsy
Molecular profiling
Live culture of patient tissue
Molecular profiling
Live culture of patient tissue
Select the right drug for the right patient
• Genetic or transcriptomic molecular signatures to identify actionable targets.
• Functional assessment of patient tumor response using whole-tissue culture techniques.
Deep correlative science to inform why treatment succeeded or failed
• Comparison of pre- and post-treatment samples to determine biological basis behind treatment success or failure.
• Can identify resistance mechanisms to inform novel therapeutics.

Figure 1 A new model of translational research using the power of deep correlative science to inform patient treatment and guide future research goals.

The discussion is led by a clinician who has taken responsibility for that patient, advocating for their wishes, and ensures MDT recommendations are followed through (Taylor et al. 2014). The MDT required to discuss a patient with pancreatic cancer should include representatives from upper gastrointestinal surgery, gastroenterologists, medical oncologists, radiation oncologists, radiologists, nuclear medicine physicians, pathologists, as well as palliative/supportive care, nursing staff, allied health (dietician, social work), genetics, and General Practitioners. The presenting clinician should be able to provide sufficient and timely information for the MDT so that treatment recommendations are well informed and more likely to be actioned (Jalil et al. 2013; Stairmand et al. 2015).

The increasing complexity of pancreatic cancer care and the implementation of multi-modality treatment highlights the value of an MDT (Maharaj et al. 2021). Despite the lack of conclusive evidence of increased survival, specialized MDT should result in increases in optimal personalized management, appropriate surgical treatment and increased clinical trial enrolment. Improved guideline adherence and patient satisfaction, reduced waiting times, and measurable changes in cancer management in up to 52% of cases are reported (Croke and El-Sayed 2012; Lamb et al. 2013).

Although all patients with pancreatic cancer should be formally presented, due to large numbers and meeting frequency, this may not be possible. More complex cases requiring multidisciplinary input should be prioritized, but registering all patients does enable monitoring of local outcomes over time as part of benchmarking of quality and safety. To ensure that no patient is disadvantaged due to geography, networked MDTs can allow access for patients and their clinicians in centers with potential lack of expertise. This can result in changes in disease stage assessment and access to multimodality (Pawlik et al. 2008) therapy by enabling greater access to these services.

Which Patients should be discussed at a Pancreatic Cancer MDT?

Ideally all patients diagnosed with pancreatic cancer should be discussed, but if resources are limited, prioritize discussion of:

- Patients with a new diagnosis of non-metastatic disease
- Recurrence with oligometastatic disease and/or unusual site of recurrence

The Role of Imaging in the Work-up of a Patient with Pancreatic Cancer

Daniel A. Moses

Medical imaging is the primary means by which the stage of pancreatic adenocarcinoma is determined. It is performed at presentation and following neo-adjuvant treatment to provide adequate staging and assessment of tumor resectability.

Staging for pancreatic adenocarcinoma is based on the TNM classification system described by eighth edition of the American Joint Committee on Cancer (AJCC) and the International Union of Cancer Control guidelines (Chun et al. 2018). Non-invasive imaging methods that can be used for diagnosis include computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). Endoscopic ultrasound (EUS) can also be used, but is more invasive.

CT is the modality of choice for diagnosis and staging due to its speed of acquisition, availability, excellent spatial resolution, and ease of standardization of scanning protocols across different vendors and institutions. It outperforms EUS and is equivalent to MRI in terms of accuracy of staging (Shrikhande et al. 2012). In respect to assessing resectability, CT has high sensitivity (87%), moderate specificity (63–75%) and highlights pancreatic lesions and vascular anatomy, in particular involvement of vascular structures around the tumor (Hong et al. 2018).

CTs’ high spatial resolution allows detection and accurate measurement of lymph nodes. Unfortunately, the low soft tissue contrast is not accurate at detecting micrometastatic deposits within lymph nodes. Therefore, the nodal staging of CT is limited, and usually related to size criteria. At a cut-off of 5 mm short axis diameter the accuracy for the detection of nodal metastatic disease is 55–60% (Shrikhande et al. 2012).

Liver metastases from pancreatic adenocarcinoma are typically hypoenhancing on the portal venous phase and CT has been shown to have a good sensitivity (70–76%) in their detection (Motosugi et al. 2011; Zhang et al. 2012). Early metastatic disease often involves the peritoneum, but is often subtle and difficult to detect on CT. This is especially true if there is background pancreatitis, for example from ERCP and stent insertion.

For the assessment of resectability and local staging of pancreatic cancer, the American College of Radiology (ACR) guidelines (Jones et al. 2017; Qayyum et al. 2017) recommend a biphasic acquisition with:

1 a late arterial phase timed to peak enhancement of the pancreatic parenchyma to maximize visualization of the primary tumor (typically 45–50 sec after the start of the IV injection).

2 a portal venous phase to optimize visualization of venous structures and detectability of hepatic metastases (typically 70 seconds after the start of the IV injection).

The sensitivity and accuracy of contrast enhanced CT for staging pancreatic adenocarcinoma is high and does not appear to vary between the different types of CT scanners (Zamboni et al. 2007). However, imaging and interpretation at high-volume centers may be more accurate (Walters et al. 2011). Without intravenous contrast CT has poor soft tissue contrast and is not useful in staging (Shrikhande et al. 2012).

EUS has variable sensitivity and accuracy for staging of pancreatic adenocarcinoma (<60% sensitivity). It is operator-dependent and therefore unable to be standardized across institutes. However, it is the most sensitive test for detecting small periampullary lesions which are undetectable on CT or MRI (Wang et al. 2013), and is best used as an adjunct or complementary modality to CT. EUS plays a larger role in diagnosis and tissue acquisition.

Advances in MRI technology over the last few years have improved spatial resolution and speed of acquisition but staging using MRI still requires an acquisition time that may extend up to 45 minutes, compared to CT of less than three minutes. MRI also has the ability to look at functional aspects of physiology and molecular processes. An important functional sequence is diffusion weighted imaging which looks at the motion of water molecules. It can detect when the diffusion of water molecules is restricted, such as in highly cellular tumors, where the intra- and extracellular spaces are small. The protocol of choice in the MRI staging of pancreatic cancer is Magnetic Resonance Cholangiopancreatography (MRCP). Contraindication to MRI include patients that have electronic or metal implants, and those that are claustrophobic. In comparison to CT, greater soft-tissue contrast can be appreciated on MRI and it is therefore far superior to staging CT when IV contrast cannot be administered, for example in the setting of renal failure. Overall, in respect to determining resectability, contrast enhanced MRCP has a sensitivity of 93% and specificity of 50% to 75% (Hong et al. 2018), MRI has greater sensitivity (up to 90%) for detecting and characterizing liver metastases when compared to contrast enhanced CT, especially when combined with hepatospecific paramagnetic gadolinium based contrast (Motosugi et al. 2011; Zhang et al. 2012).

The role of PET in staging for pancreatic adenocarcinoma is unclear (Wang et al. 2014b). It is not useful in the local staging. A recent Australian study (Burge et al. 2015) observed that PET may change management for fluorodeoxyglucose (FDG)-avid lesions; however, only about 75% of pancreatic tumors are FDG-avid. When combined with CT, PET shows increased sensitivity and changed management in 11% (Farma et al. 2008) and 16% (Burge et al. 2015) of patients.

Recommendations

- Dual phase contrast enhanced computed tomography within four weeks of diagnosis should be performed for tumor-node-metastases staging and assessing resectability before presentation to the multi-disciplinary team.
- If no metastatic disease is detected the decision about whether a tumor is resectable, borderline or nonresectable should be made by consensus at a multi-disciplinary team meeting.
- If imaging shows metastases, no further scanning is required and a biopsy should be conducted to confirm diagnosis (in this circumstance a non-dual phase CT may be acceptable).
- Staging investigations should be conducted prior to biopsy or stenting, as the presence of hematoma, stent artefact or pancreatitis reduces the ability to accurately define resectability.
- When lesions are small (<1 cm), the sensitivity of the pancreatic protocol computed tomography is reduced and the endoscopic ultrasound method should be considered to complement computed tomography results for enhanced diagnosis. Endoscopic ultrasound plays a role more so in diagnosis and tissue acquisition than in staging.
- If tissue resolution with the pancreatic protocol computed tomography is not clear (isodense pancreatic tissue or cystic lesions), or no mass is visible but the patient is jaundiced (potential liver involvement), then contrast enhanced MRCP should be performed to improve visual acuity to increase diagnostic capability for malignancy.
- MRCP and PET, if available, may be considered prior to resection or neoadjuvant therapy, to reduce risk of occult malignancy in patients with atypical radiological findings or who are biologically borderline (CA 19.9 ~500 U/ml).

Pre-operative Management

Robert C. Gandy & Koroush S. Haghighi

In the presence of a solid, resectable mass suspicious for adenocarcinoma, biopsy proof is not required before proceeding with upfront resection. Initial tissue diagnosis (using EUS biopsy) is advisable when it can be safely performed, as it may alter treatment decisions in a small number of patients, such as those with autoimmune pancreatitis (Gandy et al. 2016).

In contrast, confirmation of malignancy with biopsy is required for patients with metastatic disease, locally advanced tumors, and borderline resectable disease prior to commencing neoadjuvant therapy. Biopsy is also recommended if a neuroendocrine tumor is suspected, although Dotatate PET scan can provide an alternative approach to biopsy to confirm grade 1/2 disease.

Tissue can be taken by passing a fine-needle under EUS guidance (EUS-FNA or EUS-FNB) or under CT guidance. EUS guided tissue acquisition has a lower risk of tumor seeding and is preferred (Chen et al. 2012).

Successful predictors of diagnostic yield of EUS-guided biopsy in pancreatic cancer include:

- experience of endoscopist
- number of passes of needle through tumor
- type of needle used (fine needle biopsy (FNB) vs fine needle aspiration)
- presence of onsite cytologist/cytopathologist.

Ongoing research to improve the diagnostic accuracy of EUS-FNA is ongoing. The presence of a cytologist during the biopsy procedure improves diagnostic yield (Iglesias-Garcia et al. 2011; Khan et al. 2017).

Pre-operative Biliary Stenting

- **Patients considered for upfront surgery**

Preoperative decompression of the biliary system should be performed selectively on a case-by-case basis, factoring in surgical timing and preferably endoscopically. Considerations include biliary sepsis or active coagulopathy, total bilirubin levels of 20 mg/dl or 340Umol/l, or when there is a need for pre-surgical optimization or extended evaluation that may delay surgery beyond two weeks. Multiple randomized trials have been conducted in patients with potentially resectable pancreatic cancer and malignant obstructive jaundice, with one suggesting benefit for preoperative biliary drainage, but the remaining eight concluding potential harm from sepsis related morbidity or no benefit (Bonin and Baron 2011).

- **Patients considered for neoadjuvant therapy**

When neoadjuvant treatment is considered, preoperative stenting is mandatory to reduce the risk of interruption of systemic therapy (Seo et al. 2019). Biliary stenting also restores GI continuity and improves nutrition over an extended treatment period. Short uncovered or partially covered metal stents outperform plastic stents and can be removed at subsequent surgery.

Laparoscopy

Staging Laparoscopy

Small hepatic or peritoneal metastases, which are not evident from the preoperative studies, may be found at surgical exploration in 8–15% of cases. As an example, 117 of 1423 pancreatectomies (8%) intended for resection of pancreatic ductal adenocarcinoma were aborted, most often due to occult liver (79%) or peritoneal metastasis (16%) (Gemenetzis et al. 2019).

For this reason, many surgeons prefer to begin cancer operations with laparoscopy, which permits examination of the liver and peritoneal surfaces and biopsy of any suspicious areas, avoiding inappropriate laparotomy. A drawback is the inability to determine whether any vascular invasion has occurred that precludes resection, accordingly we restrict the use of laparoscopy to cases with a high likelihood of unresectability, including the suspicion of lymph node metastasis not proven on biopsy, indeterminate liver lesions, the presence of peritoneal fluid or raised ca 19–9 above 250 U/ml (Gemenetzis et al. 2019).

Pancreatic body and tail tumors have higher rates of occult peritoneal metastasis and may warrant laparoscopy prior to laparotomy. Timing of diagnostic laparoscopy can be prior to trial of dissection and peritoneal washings may be performed then or immediately prior to laparotomy.

Laparoscopy Prior to Neoadjuvant Therapy

In contrast to resectable disease, borderline resectable pancreatic cancer (BRPC) is associated with higher rates of occult metastatic disease (up to 25% of cases). In this setting, laparoscopy to perform peritoneal washings and biopsy of suspicious lesions may be beneficial. Following neoadjuvant therapy, laparoscopy prior to laparotomy in BRPC and locally advanced pancreatic cancer (LAPC) can also reduce the non-therapeutic laparotomy rate in between 20 and 36% respectively and can fail to detect metastatic disease in only 5% of cases (Peng et al. 2017; Ta et al. 2019).

Perioperative Care

Robert C. Gandy & Koroush S. Haghighi

A surgical treatment pathway is currently considered to be the only potentially curative option for pancreatic adenocarcinoma. At a minimum this includes surgery and adjuvant chemotherapy, and confers both high morbidity and the risk of perioperative mortality. Given the potential adverse impact, a surgical pathway should be reviewed by a specialist multi-disciplinary team whose role is to reduce rates of futile or non-therapeutic surgery.

Assessment

Referral pathways to pancreatic surgeons differ between healthcare systems around the world. In our own setting, patients with suspected pancreatic malignancy are often referred to surgical teams for diagnosis, work-up, and therapy, whereas in other regions referral to a pancreatic surgeon may take place only after work-up is complete or even following induction therapy. However, it is important for pancreatic surgeons to make a complete assessment prior to initial MDT meeting and therapy. Decision-making regarding the surgical pathway chosen depends on clinician's assessment of the resectability of the disease and whether localized disease is determined to be:

Definitions

Resectable: These are tumors in which a successful pancreatectomy could be completed with clear margins and lower risk of early recurrence.

Borderline resectable: These are tumors with substantial risk of positive margins or lymph node metastasis if surgery was considered upfront.

Locally advanced: These are tumors that have not metastasized but are initially inoperable but may be down staged or downsized, allowing successful surgery with clear margins.

A patient may be borderline resectable based upon anatomical (A), biological (B), or conditional (C) elements alone, or in combination, as initially proposed by MD Anderson Cancer Center (Isaji et al. 2018).

Clinical Assessment, Pre-optimization and Preparation for Multidisciplinary Presentation

Clinical assessment plays a critical role, minimum information required includes the duration of illness, important red flag symptoms, and signs for advanced disease such as back pain or extensive weight loss. Clinicians should also have had extensive discussion with patients and family members regarding their treatment wishes, so they may advocate on their behalf at an MDT. It is important for clinicians to arrange a pancreatic protocol computed tomography (PPCT) scan of the chest and abdomen, tissue biopsy and bile duct stenting, when appropriate (see below) and preoperative blood tests should include liver function, renal function, diabetic function, and tumor markers, prior to initial MDT (Gandy et al. 2016).

Patients being assessed for pancreatic surgery often have significant medical comorbidities. Since most resections are performed electively, adequate time is available to assess risk factors and optimize the patient's medical status. Early assessment in a pre-anesthetic clinic gives the opportunity to mitigate any risk factors, through specialist optimization of known organ dysfunction. Formal nutritional assessment and early dietetics intervention may help prevent weight loss in the peri-operative period (early intervention in the form of stenting, enteral, or even parenteral feeding, may be required). Functional assessment with a specialist physiotherapist and pre-habilitation may improve outcomes of pancreatectomy but given time constraints may be most suited to patients undergoing neoadjuvant therapy. Patients who are considered borderline resectable on conditional grounds may become resectable following medical optimization (Bundred et al. 2020).

The median age of diagnosis of pancreatic cancer patients is 70 years and with life expectancy increasing, a considerable proportion of patients will experience frailty syndrome. Frailty has a significant impact on outcomes of pancreatic surgical pathways and patients' ability to undergo adjuvant or neoadjuvant therapy. The clinical frailty score (CFS) is a simple and easy-to-use screening tool for patients undergoing surgical pathways such as pancreatectomy for pancreatic adenocarcinoma (Mcisaac et al. 2020). High CFS scores correlate with survival as well as being a predictor of peri-operative morbidity and new disability following surgery (Yamada et al. 2021).

However, the implementation of integrated surgical care of older patients with surgeons and geriatricians mitigates the effects of perioperative delirium and reduces complications (Norris and Close 2020).

Initial Multidisciplinary Meeting (Non-metastatic Pancreatic Adenocarcinoma)

In comparison to other tumor streams, where the TNM staging system is estimated clinically and radiologically, non-metastatic pancreatic cancer is preoperatively staged by its resectability status. The treatment pathway may vary greatly on this assessment. Of key significance is the appreciation and agreement on what constitutes borderline resectability based on the anatomical dimension of tumor-vessel relationship, including elements related to biological factors of the tumor, and conditional factors of the host.

Assessment of Resectability

Operable/resectable Pancreatic Cancer

Anatomically resectable disease under the international consensus is characterized by no tumor contact with arterial structures and up to 180 degree contacts with the superior mesenteric vein (SMV)/portal vein (PV) confluence or unilateral narrowing of the SMV/PV confluence only. Limited vein contact on imaging is not an independent risk factor for survival but is associated with higher margin positivity (up to 35%) and the need for venous resection and reconstruction (Tran Cao et al. 2014; Yamada et al. 2013).

Borderline Resectable Pancreatic Cancer

In 2016 the international consensus definition of borderline resectable pancreatic cancer defined three distinct areas for the assessment of non-metastatic disease (Isaji et al. 2018).

A Anatomical factors of the disease: the tumor in relation to the loss of fat planes between adjacent organs and major blood vessels.

B Biological: suspicion for metastatic disease despite appearing resectable based on anatomic criteria.

C Conditional: patients with poor performance or comorbidity, but otherwise resectable disease based on Anatomic and Biological criteria.

Biological Factors

Patients were considered to have BRPC (low probability to achieve resection with 1 mm clear margin but possible) based on pancreatic protocol CT scan. The BRPC classification is supported by the overall survival difference between the groups observed, when compared to clearly resectable tumours, of 27.8 to 44.5 months (Tran Cao et al. 2014). For the purposes of classification and benchmarking borderline resectable disease is further subdivided into BR-PV, or BR-A based on involvement of SMV/PV and/or arterial structures, respectively (Gandy et al. 2016; Isaji et al. 2018).

In addition to standard axial measurement of degree, a formal longitudinal or cephalocaudal assessment of extent, specifically in relation to the inferior margin of the duodenum. This is employed to address the issue whether safe and successful portal vein reconstruction can be performed. Venous involvement below this level is classified unresectable and locally advanced and is now widely adopted.

The next element in consideration of vascular involvement (in addition to circumference and length) is the resultant effect of such involvement on venous flow or arterial anatomy. Bilateral narrowing of the SMV/PV, or occlusion of these veins equates to BR-PV disease (in the absence of extension beyond the inferior border of the duodenum) (Tempero et al. 2021).

Similarly, stenosis or deformity of arterial structures upstages contact with the coeliac axis or SMA of less than 180° (BR-A) to locally advanced. Arterial involvement of the common hepatic artery may be considered borderline resectable (so long as there is no tumor contact with the proper hepatic artery and/or the coeliac axis).

Biological Factors Includes a High Degree of Suspicion for Metastatic Disease despite Appearing Resectable Based on Anatomic Criteria

In this context, "borderline" may be referring to an individual patient's likelihood of benefit from upfront surgery and indicate a preference for systemic therapy as first line treatment, followed by restaging prior to proceeding to surgery where appropriate. Such factors include – clinical findings suspicious (but unproven) of distant metastases, regional lymph nodes metastases (Ozaki et al. 1999) diagnosed by EUS biopsy, or positron emission tomography-computed tomography 24, or high CA 19.9 level (in the absence of hyperbilirubinemia). International consensus agreed on a threshold value of 500 IU/mL as the level above which a patient may be categorized as BR-Type B based on a study demonstrating lower resection rate and lower median survival time after resection at that cut-point (Khorana et al. 2019). Such patients may be at most of "borderline-benefit" from upfront surgery without preoperative systemic therapy.

Conditional Factors Includes Patients that May Require Initial Optimization

The final element by which a patient with anatomical clear resectability, and no suspicion of micro metastatic disease may be considered to be at risk of borderline benefit is in their ability to withstand the surgical rigor of pancreaticoduodenectomy (borderline resectable on conditional grounds – BR-Type C).

Based on Eastern Co-operative Group (ECOG) performance status (PS), with data showing PS of 2 associated with significantly shorter median survival for all resectable stages of pancreatic cancer (Tas et al. 2013) compared with ECOG 0 or 1 as does major co-morbidity .

However, some patients with BR-Type C disease may be rendered fit for surgery with appropriate medical optimization, nutritional support, or pre-habilitation (Tzeng et al. 2014).

We have found this "A, B, C" framework useful for use in multidisciplinary meetings when assessing cases of non-metastatic pancreatic cancer, as borderline resectability has a large bearing on choice of surgical pathway; with such patients often being considered for neoadjuvant therapy.

Locally Advanced Pancreatic Cancer

Disease considered inoperable (unable to achieve R0, without downstaging) due to proven extensive (including macroscopic para-aortic and non-regional) lymph node metastasis or tumor involvement with veins and arteries beyond that defined as borderline resectable. Around 25% of patients may become resectable with extensive neoadjuvant chemotherapy (Kunzmann et al. 2019).

Limitations of Conventional Imaging

Pancreatic tumors are often poorly visualized on conventional imaging such as MRI and CT imaging. PET scan and endoscopic ultrasound may give additional information in respect to the nature of enlarged or suspicious lymph nodes or the interface of major vasculature (Luz et al. 2014; Wang et al. 2014b). Contrast enhanced MRI with liver specific contrast may also provide more information of suspicious lymph nodes (Motosugi et al. 2011). Small volume peritoneal deposits are difficult to determine on preoperative imaging and are one of three primary reasons for non-therapeutic laparotomy. Staging laparoscopy may be beneficial to reduce the risk of non-therapeutic laparotomy as described above.

Re-imaging after Neoadjuvant Therapy

The primary purpose of repeat imaging prior to surgery is to rule out metastatic disease, multiple studies have shown that while response to treatment (using the resist criteria) is a good predictor of future resectability, lack of response using conventional imaging does not predict non-resectability in borderline cases (Beleù et al. 2019; Katz et al. 2012; Xia et al. 2017). In the setting of locally advanced disease lack of response again does not predict unresectable disease, but attention should be paid to feasibility of vascular reconstruction. To date the best predictor of response and complete pathological response is the normalization of tumor marker Ca 19–9, notwithstanding its own limitation (Boone et al. 2014; Ferrone et al. 2015; Truty et al. 2021).

Pancreaticoduodenectomy Technique

Minimally invasive pancreaticoduodenectomy has acceptable outcomes in selected patients. In expert high-volume centers, it may be associated with reduced length of stay and earlier time to adjuvant therapy (Sharpe et al. 2015; Stauffer et al. 2017).

Extended Pancreatectomy

Extended pancreatectomy remains an area of controversy and the evidence supporting the utility of extended resection has many confounding factors. Despite the potential for increased peri-operative morbidity (Casciani et al. 2021), the benefits of extended pancreatectomy mean a greater proportion of patients undergo potentially curative treatment and may be best applied following a neoadjuvant pathway as tumors are usually larger and have adverse features, which affect survival (Hartwig et al. 2014; Wang et al. 2014a).

Venous Resection

Patients with up to 180-degrees contact venous abutment on preoperative imaging may have, true portal vein invasion observed in 41%, whereas over 180-degree venous involvement, distortion or occlusion of the vessel results in rates of true PVI are much higher (59%). Even tumors with no porto-mesenteric venous contact on CT scanning have very low rates of true portal vein invasion, only 6% (Tran Cao et al. 2014; Yamada et al. 2009).

This is evidenced by a positive margin rate (R1 = 0 mm) which is significantly lower in the no vein contact group, 24% versus 34% when vein contact is observed, despite an additional 65% of patients requiring vein resection, when tumor contact of the vein was present on imaging (Zhou et al. 2012, Yamada et al. 2013). Patients undergoing PV and SMV resections generally have similar mortality and morbidity to patients who have standard resections (Murakami et al. 2015; Ravikumar et al. 2014).

This has great implications for the surgical management of patients with resectable tumors, the need for portal vein resection mandates the ability for pancreatic surgeons to perform venous resection and reconstruction, even when unexpected. The argument against venous resection is that true portal vein involvement is associated with poor survival (irrespective of successful venous resection) and that patients without true portal vein involvement do not require vein resection, effectively rendering the procedure to have limited benefit. However, venous resection may also aid clearance of the critical posterior margins and the SMV/SMA groove. Vein resection is also associated with less bleeding and less potential for catastrophic bleeding when compared to stripping of a tumor from an involved or densely adhered vessel and the outcomes of SMV/PV resection are significantly better than R2 resection.

Arterial Resection

In contrast, due to the high mortality and high local failure rates, resection of the SMA is only recommended in exceptional circumstances, as there is a paucity of data to support arterial resection increasing survival over palliative chemotherapy. In exceptional circumstances, and following a period of neoadjuvant therapy and multidisciplinary approval, arterial resection may be appropriate (Bockhorn et al. 2014; Ouaïssi et al. 2014).

Palliative Surgery in Obstructing Periampullary Tumors

In up to 25% of cases of pancreatic cancer patients will present with obstruction of the duodenum or bile duct. Of these 50% will present with metastases at presentation. The gold standard for palliation of the effects of gastric outflow obstruction and bile duct obstruction was "double bypass surgery" consisting of open hepaticojejunostomy and gastrojejunostomy. These procedures carry a 2% mortality and up to 35% morbidity. However, they render the best functional outcomes for patients and may be more durable.

Endoscopic stenting procedures have largely replaced palliative surgical options for obstructed pancreatic cancer. Endoscopic biliary stenting is feasible in over 90% of cases and is associated with low morbidity, low rates of mortality, reduced length of stay, and a higher proportion of patients receiving systemic chemotherapy. For patients diagnosed with metastatic disease at presentation we recommend endoscopic stenting of any biliary and duodenal obstruction.

For patients who have proceeded to laparotomy (without prior endoscopic stenting) and the finding of unresectable disease or low volume metastatic disease the recommendation is less clear. This group of patients may inherently have a better prognosis, than those with grossly metastatic disease. In the metastatic setting, biliary and gastric bypass procedures are associated with increased time to systemic therapy compared non-therapeutic surgical exploration (Azari et al. 2020). For patients diagnosed with unresectable disease at surgical exploration via laparotomy surgical bypass is a reasonable option. If metastatic disease is encountered conferring a worse prognosis nontherapeutic surgery and subsequent endoscopic stenting is preferred. However, this should be judged by the operating surgeon on a case-by-case basis.

Systemic Therapy

Omali Pitiyarachchi & David Goldstein

Neoadjuvant Therapy

Neoadjuvant therapy is utilized in borderline resectable and locally advanced pancreatic cancer to downstage tumors allowing resection in 6–60% of cases (Gemenetzis et al. 2019; Hackert et al. 2016; Lakatos et al. 2017; Rombouts et al. 2016). Ability to undergo surgical resection translates to a significantly improved OS (Gemenetzis et al. 2019; Kunzmann et al. 2019). Only 50–60% of patients complete adjuvant chemotherapy (Barbour et al. 2020; Baugh et al. 2019; Mayo et al. 2012; Tran Cao et al. 2017), which adds to the appeal of neoadjuvant therapy. There is no negative impact on surgical outcome identified for patients with likely moderate to severe poor outcomes with upfront surgery (Barbour et al. 2020; Da Costa et al. 2020; Sohal et al. 2021), with the added benefit of downstaging cN1 patients to ypN0 (Tran Cao et al. 2017). Survival data will be available with randomized trials soon.

Locally Advanced Disease

Quality randomized data is lacking, but conversion to surgical resection after neoadjuvant therapy is possible in 20–30% of patients (Gemenetzis et al. 2019; Kunzmann et al. 2019; Suker et al. 2016) with apparent improved median OS in those resected (Gemenetzis et al. 2019; Kunzmann et al. 2019). The NEOLAP trial (Kunzmann et al. 2019) showed a 30.6% conversion rate to surgery in the gemcitabine + nab-paclitaxel arm and 45% in the FOLFIRINOX arm (OR 0.54; 95% CI, 0.26–1.13; p=0.135) with a statistically significant improved in OS of 27.4 months compared to 14.2 months for patients unable to have surgical resection (p=0.0035). Similarly, in another study (Gemenetzis et al. 2019), the median OS was 19 months greater (35.3 mo vs 16.3 mo; p< 0.001) in patients able to undergo surgical resection after FOLFIRINOX-based neoadjuvant therapy.

For patients with poor performance status and locally advanced disease, consider single agent chemotherapy with gemcitabine (Glimelius et al. 1996), or palliative radiation for local symptom control. Alternatively, consider best supportive care if the patient is unsuitable for chemotherapy or radiotherapy. Also refer to the **Radiation** section for the use of radiation in locally advanced disease.

Borderline Resectable Disease

Multimodality neoadjuvant therapy should be considered in patients with borderline resectable pancreatic cancer. The results of ESPAC-5F (Ghaneh et al. 2020), which was designed to show feasibility of neoadjuvant therapy showed promising results. Ninety-nine patients were randomized to four groups, upfront surgery, gemcitabine/capecitabine, FOLFIRINOX, and chemoradiation (capecitabine). Although not statistically significant, the R0 resection rate for patients that received neoadjuvant therapy was 23% compared to 15% for patients that had upfront surgery (p=0.721). Survival at one year was higher for neoadjuvant therapy, 77% vs 40% for upfront surgery (p<0.001), although not powered for this. Similarly, the proportion of patients converted to surgical resection was 67.8% in a meta-analysis which included 313 patients who received neoadjuvant FOLFIRINOX. In those patients, 83.9% of patients achieved a R0 resection, and a median OS of 22.2 months (Janssen et al. 2019).

PREOPANC-1 trial (Versteijne et al. 2022) which evaluated neoadjuvant chemoradiation (gemcitabine) showed a slightly better mean OS of 1.4 months (15.7months v 14.3 months) [HR 0.73; 95% CI, 0.56–0.96; p=0.025], but the five-year OS rate was substantially greater with neoadjuvant therapy (20.5% v 6%). The trial randomized 246 patients with resectable or borderline resectable pancreatic cancer to either upfront surgery followed by six cycles of adjuvant gemcitabine, or neoadjuvant CRT with gemcitabine, followed by resection and four cycles of adjuvant gemcitabine. The benefit from neoadjuvant chemoradiation led to the early termination of a Phase II/III study (Jang et al. 2018) comparing neoadjuvant chemoradiation with gemcitabine to upfront surgical resection. Nevertheless, it showed a two-year survival rate with chemoradiation of 40.7% compared to 26.1% with upfront surgery, and an improved mOS of 21 months compared to 12 months with upfront surgery [HR 1.495, 95% CI 0.66–3.36; p = 0.028]. A greater proportion of patients achieved an R0 resection in the neoadjuvant arm (52.5%) compared to 26.1% in the patients that had upfront surgery.

This encouraging data is being further explored, in the ongoing phase 3 PREOPANC-2 study which updated the neoadjuvant chemotherapy regimen to FOLFIRINOX. Patients are randomized to eight cycles of neoadjuvant FOLFIRINOX followed by surgery, to neoadjuvant CRT with gemcitabine, followed by surgery and four cycles of adjuvant gemcitabine. In addition, MASTERPLAN, an AGITG-sponsored randomized Phase II study, is exploring the safety and efficacy of adding stereotactic body radiotherapy (SBRT) to three months of neoadjuvant chemotherapy, in patients with high risk, borderline resectable or locally advanced pancreas cancer (Oar et al. 2021). The results of both these trials are awaited.

Consequently, neoadjuvant therapy is recommended for patients with borderline resectable pancreatic cancer, due to the high conversion rate for surgical resection which is related to improved overall survival (Tempero et al. 2019). It is reasonable to use either mFOLFIRINOX or gemcitabine/nab-paclitaxel in patients with a good performance status. Currently, the practice is to give all neoadjuvant treatment prior to surgery, but this may change to a perioperative approach in future.

Resectable Disease

The evidence for the use of neoadjuvant therapy in patients with resectable disease is evolving. A meta-analysis which included 38 studies (principally Phase II randomized) and 1738 patients who had neoadjuvant treatment for resectable and borderline resectable pancreatic cancer (Versteijne et al. 2018) showed an improved OS in the intention to treat population of 18.8 months compared to 14.8 months for those who had upfront surgery. Interestingly, the resection rate was lower in patients who had neoadjuvant therapy (66% v 81.3%), but a higher R0 rate was achieved (86.8% v 66.9%). This data is mainly from phase II randomized trials.

The Italian Phase II trial PACT-15 showed an improved OS of 38 months with 3 cycles of preoperative and postoperative PEXG (cisplatin, epirubicin, gemcitabine, and capecitabine), as compared to the two arms which received adjuvant chemotherapy, which was 20 months in the adjuvant gemcitabine arm, and 26 months in the adjuvant PEXG arm (p-value not reported) (Reni et al. 2019). The Japanese Prep-02/JSAP-05(Motoi et al. 2019) study showed a clear survival benefit with neoadjuvant therapy, with a median OS of 36.7 months in the patients who received neoadjuvant gemcitabine/S-1 chemotherapy, and 26.6 months for the patients who had upfront surgery [HR 0.72 (95% CI, 0.55-0.94; p=0.015)]. A Phase II randomized trial of mFOLFIRINOX compared with gemcitabine/nab-paclitaxel in resectable pancreatic cancer (Sohal et al. 2021) showed similar two-year overall survival rates (47% v 48%) and mOS (23.2 months v 23.6 months), and resection rates (73% v 70%). mDFS after resection was 10.9 months v 14.2 months favoring the gemcitabine/nab-paclitaxel arm.

The deliverability of chemotherapy may be more feasible in the neoadjuvant setting, as shown in the phase 2 AGITG GAP study with 93% of patients completing two cycles of neoadjuvant chemotherapy with gemcitabine/nab-paclitaxel, compared to 63% of patients who completed all four cycles of postoperative chemotherapy (Barbour et al. 2020). Achieving an R0 resection translated to an increase in mOS of a further 10 months compared to an R1 resection.

To date, there is no Phase III RCT data supporting the use of neoadjuvant therapy in patients with resectable pancreatic cancer. It should only be considered in the setting of a clinical trial.

Summary of Indications for Neoadjuvant therapy

Resectable

- Neoadjuvant therapy remains unproven and should be explored within clinical trials.

Borderline resectable

- Neoadjuvant therapy should be recommended.
- The recommended chemotherapy regimens are (m)FOLFIRINOX, or gemcitabine + nab-paclitaxel.
- Neoadjuvant CRT has the most compelling mature randomized data with an improved OS and R0 resection rate.

Locally advanced

- Consider enrolling the patient in a clinical trial
- 20–30% of patients who undergo neoadjuvant therapy may convert to surgical resection
- Chemotherapy, chemoradiation, or a combination can be considered

Adjuvant Therapy

For all patients who did not receive neoadjuvant therapy, the current guidelines, including ASCO (Khorana et al. 2019), ESMO (Ducreux et al. 2015), and NCCN (Tempero et al. 2021) recommend six months of adjuvant therapy. These are summarized in the Table below. A new baseline CT of the chest, abdomen and pelvis post-surgery, and CA19.9 measurement should be performed. If metastatic disease is not identified, then adjuvant therapy is recommended, and should commence within 12 weeks of surgical resection. The preferred options are for adjuvant chemotherapy, or a combination of chemotherapy ± chemoradiation. As completion of six months of adjuvant chemotherapy is an independent prognostic factor for overall survival, so adequate time should be given for the patient to recover from surgery but still commence within the 12-week window (Valle et al. 2014). The options for chemotherapy include modified FOLFIRNOX (Conroy et al. 2018), gemcitabine/capecitabine (Neoptolemos et al. 2017), or gemcitabine monotherapy (Oettle et al. 2013) [see Table below]. FOLFIRINOX is suitable for patients with an excellent performance status. If a patient has a borderline performance status or comorbidities which would limit multi-agent chemotherapy, gemcitabine monotherapy is preferred. If a patient is unsuitable for platinum-based chemotherapy, such as the presence of peripheral neuropathy, then the combination of gemcitabine and capecitabine is used.

Summary of adjuvant systemic therapy for resected pancreatic cancer

Study	ESPAC-4 (Neoptolemos et al. 2017, Neoptolemos et al. 2020)	PRODIGE-24 (Conroy et al. 2018)	CONKO-001(Oettle et al. 2013, Oettle et al. 2007)
Population	Complete macroscopic resection R0 or R1		
Regimen[a]	Gemcitabine + capecitabine	mFOLFIRINOX	Gemcitabine
Comparator arm	Gemcitabine	Gemcitabine	Observation
Duration of treatment	6 mo	6 mo	6 mo
Median follow-up	60 mo	33.6 mo	136 mo
Median OS	27.7 mo v 26 mo (5-yr survival 28% v 20%; HR=0.84 [95% CI, 0.70 – 0.99]; *P*=0.049)	54.5 mo v 35 mo HR 0.64 [95% CI, 0.48 to 0.86; P=0.003]	22.8 mo v 20.2 mo HR 0.76 [95% CI, 0.61–0.95; *P*=0.01]

In Australia, modified FOLFIRINOX tends to be used over standard FOLFIRINOX (Conroy et al. 2018). Of note, the trial included patients up to age 79 in the mFOLFIRINOX arm, with 19% of patients aged 70 or over. There was no difference in adverse events from treatment between the treatment arms in older patients (age ≥70 years).

The evidence for combination gemcitabine and capecitabine comes from the ESPAC-4 trial (Neoptolemos et al. 2017). Five-year OS data showed 28% overall survival with gemcitabine/capecitabine compared with 20% in the gemcitabine only arm [HR 0.84; 95% CI, 0.70 – 0.99; p=0.049]. Adjuvant gemcitabine doubles OS with gemcitabine (20.7%) compared to observation (10.4%) (Oettle et al. 2013) at 5 years, and the benefit is maintained at 10 years (OS 12.2% GEM v 7.7% OBS).

The use of nab-paclitaxel/gemcitabine in the adjuvant setting was evaluated in APACT. This study did not meet its primary end point of DFS as assessed by independent review (Reni et al. 2019). The authors commented that the DFS in the gemcitabine arm was higher than historical controls, and the use of independently assessed as opposed to investigator assessed endpoints may have had an impact.

There is no conclusive evidence for adjuvant therapy in patients who received neoadjuvant therapy, with no RCT showing that further chemotherapy beyond six months of neoadjuvant or perioperative chemotherapy has any benefit. Chemoradiation for those patients with a positive R1 resection margin and/or positive lymph node after preoperative therapy can be considered (Khorana et al. 2019) but there is no randomized evidence supporting this approach.

Other Considerations for Systemic Therapy

The most common mutations in familial pancreatic cancer are *BRCA1* and *BRCA2*, detected in 2–3% (Petersen 2016; Young et al. 2018) of patients with pancreas cancer, with higher rates seen in patients of Ashkenazi Jewish heritage (Pilarski 2019). Recent data suggests platinum sensitivity of *BRCA*-mutated PDAC (Kowalewski et al. 2018).

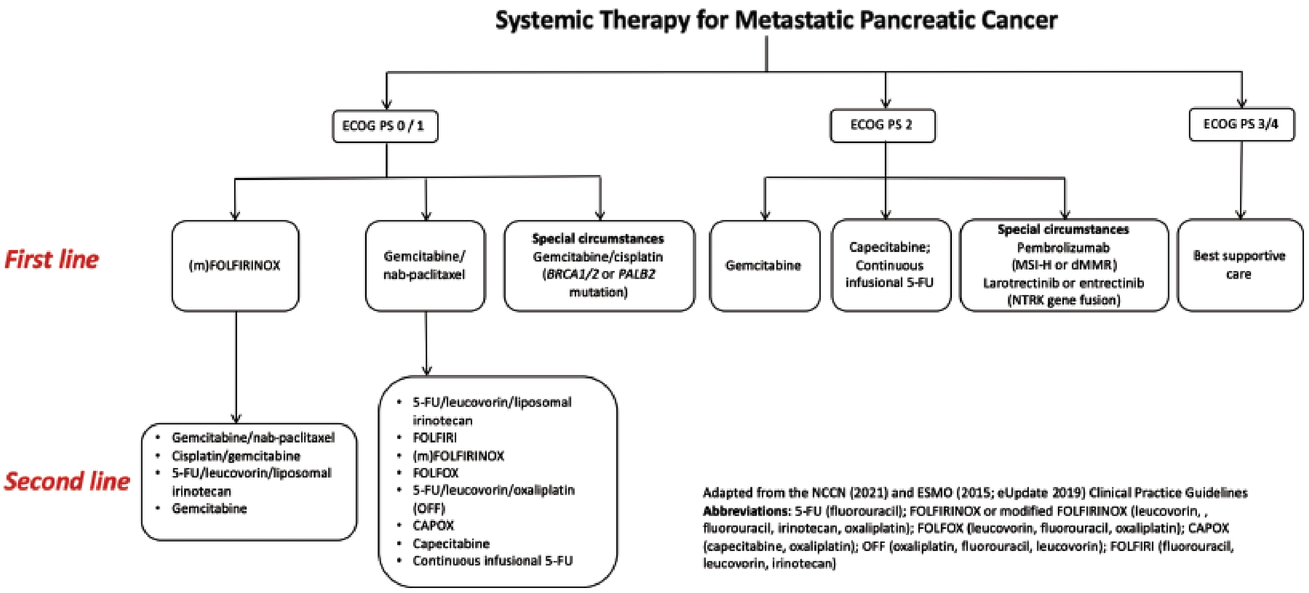
The use of a PARPi as maintenance treatment has been evaluated in a phase 3 trial for patients with PDAC associated with a germline BRCA mutation (POLO – (Golan et al. 2019)). In this trial, after an initial response of at least stable disease to upfront platinum-based chemotherapy of at least 16 weeks' duration; patients were randomized to receive either Olaparib or placebo. Patients in the Olaparib arm had a higher PFS of 7.4 months compared with 3.8 months in patients who received placebo (HR 0.53, 95% CI 0.35, 0.82; p = 0.004), however there was no significant difference in median OS at median 31-month follow-up – 19.0 months in the olaparib arm compared to 19.2 months with placebo (HR 0.83, 95% CI 0.56, 1.22; p = 0.3487).

A combination approach of a PARPi with chemotherapy in the upfront setting for advanced PDAC (Stage III/IV) was evaluated with veliparib in the phase II trial with gemcitabine and capecitabine. There was no statistically significant benefit to the addition of veliparib to chemotherapy (O'Reilly et al. 2020).

An emerging option is the combination of PARPi with ICI which has shown promising results in a proof-of-concept study (Lampert et al. 2020). The combination of Olaparib with the PD-1 inhibitor pembrolizumab as maintenance therapy after platinum based chemotherapy is being evaluated in a randomized phase II trial SWOG S2001 [NCT04548752].

Metastatic Disease

It is important to discuss the goals of care at the outset of a patient diagnosed with metastatic PDAC and early referral to palliative care service is recommended. Enrolment in a clinical trial should be considered for all patients deemed suitable by the treating clinician. Other considerations include performance status, patient preference for systemic therapy, cancer-related symptoms, comorbidities, impact of disease on quality of life and psychological status, and support systems (Sohal et al. 2016). A suggested treatment algorithm is shown in Figure 2. Best supportive care is recommended for patients with a poor performance status (ECOG PS 3) and comorbidities which impact treatment, but systemic therapy can be considered for individual patients. Biliary obstruction should be relieved with stenting as required, and adequate liver function is required for administration of systemic therapy. Many published studies allow bilirubin levels up to 1.5 times the upper limit of normal (Conroy et al. 2011). The use of immune checkpoint


Systemic Therapy for Metastatic Pancreatic Cancer
ECOG PS 0 / 1
ECOG PS 2
ECOG PS 3/4
First line
(m)FOLFIRINOX
Gemcitabine/ nab-paclitaxel
Special circumstances Gemcitabine/cisplatin (BRCA1/2 or PALB2 mutation)
Gemcitabine
Capecitabine; Continuous infusional 5-FU
Special circumstances Pembrolizumab (MSI-H or dMMR) Larotrectinib or entrectinib (NTRK gene fusion)
Best supportive care
Second line
Gemcitabine/nab-paclitaxel
Cisplatin/gemcitabine
5-FU/leucovorin/liposomal irinotecan
Gemcitabine
5-FU/leucovorin/liposomal irinotecan
FOLFIRI
(m)FOLFIRINOX
FOLFOX
5-FU/leucovorin/oxaliplatin (OFF)
CAPOX
Capecitabine
Continuous infusional 5-FU

Adapted from the NCCN (2021) and ESMO (2015; eUpdate 2019) Clinical Practice Guidelines
Abbreviations: 5-FU (fluorouracil); FOLFIRINOX or modified FOLFIRINOX (leucovorin, , fluorouracil, irinotecan, oxaliplatin); FOLFOX (leucovorin, fluorouracil, oxaliplatin); CAPOX (capecitabine, oxaliplatin); OFF (oxaliplatin, fluorouracil, leucovorin); FOLFIRI (fluorouracil, leucovorin, irinotecan)

Figure 2 Systemic therapy for metastatic pancreatic cancer.

inhibitors and NTRK inhibitors are discussed in the previous section (Other considerations for systemic therapy).

For patients with comorbidities impacting treatment or ECOG PS 2, either gemcitabine monotherapy (Burris et al. 1997), capecitabine or infusional 5-fluourouacil can be used as per the NCCN (Tempero et al. 2021) and ESMO Guidelines (Ducreux et al. 2015). In certain cases, such as young patients with ECOG PS 2 and no comorbidities, a more intensive regimen may be considered as per the clinician's discretion. FOLFIRINOX (or modified FOLFIRINOX) should be offered to patients with a good performance status (ECOG PS 0 or 1) and well-controlled comorbidities (Conroy et al. 2011). Median OS was greater in patients who received FOLFIRINOX (11.1 months v 6.8 months) compared to gemcitabine [HR 0.57; 95% CI, 0.45 – 0.73; p=0.001]. Of note, only patients up to age 75 were enrolled in this study so the use of FOLFIRINOX/mFOLFIRINOX in older patients should be carefully considered. Gemcitabine/cisplatin can be considered for patients with a *BRCA1/2* or *PALB2* mutation as an alternate platinum containing regimen.

An alternative first-line therapy is gemcitabine/nab-paclitaxel (Von Hoff et al. 2013). In this study, median overall survival was greater for patients who received gemcitabine/nab-paclitaxel compared with patients who received gemcitabine alone (8.5 months vs 6.7 months) [HR, 0.72; 95% CI, 0.62 to 0.83; p=0.001]. Common Grade 3/4 toxicities include neutropenia, fatigue, peripheral neuropathy, febrile neutropenia, and diarrhea.

Based on expert consensus recommendations, patients who received FOLFIRINOX as first-line treatment can be offered gemcitabine/nab-paclitaxel as second-line therapy, and vice versa, as long as their performance status and comorbidities allow further systemic therapy (Sohal et al. 2016). Other second line therapies can be offered to patients with an adequate performance status allowing further systemic therapy (ECOG PS 2). Selected patients who have progression at single sites may benefit from chemoradiation (Tempero et al. 2021).

Immune checkpoint inhibitor therapy may be considered for patients with MSI-H/dMMR pancreatic cancer (Marabelle et al. 2020). On the basis of the results of basket trials, larotrectinib (Drilon et al. 2018), and entrectinib (Doebele et al. 2020) have been approved for patients with NTRK gene fusions. As there is currently no evidence guiding duration of therapy, this should be guided by patient preference for continued systemic therapy, response to treatment, and toxicity of therapy (Sohal et al. 2016).

Radiation Therapy

Stephen R. Thompson

The only curative treatment for pancreatic cancer is surgery, but as discussed above, only 20–30% of patients will have resectable disease (Butturini et al. 2008). The role of radiation therapy (RT) is controversial, and can be classified as definitive for locally advanced disease, neoadjuvant or adjuvant in addition to surgery, or palliative for medically unfit patients or in the presence of metastatic disease (Tempero et al. 2021). Each of these will be outlined below, including a summary of the highest quality data available, RT approaches, and results.

Locally Advanced Pancreatic Cancer

For those patients with LAPC, the mainstay of management is with palliative chemotherapy (Tempero et al. 2021). Data regarding the potential additional benefit of adding RT has been confounded by a lack of high quality randomized evidence, with those few randomized studies that have been performed being antiquated and/or underpowered (Hazel et al. 1981; Klaassen et al. 1985; Loehrer et al. 2011) or detrimental with irradiation that was too toxic (60Gy with concurrent cisplatin/5FU) (Chauffert et al. 2008). One large, modern trial has been conducted: LAP07 (Hammel et al. 2016), showing that after 16 weeks of induction gemcitabine (allowing time for the potential early development of metastatic disease), chemoradiotherapy with capecitabine (830mg/m2 BD on RT days) to 54Gy in 30 fractions targeting the gross tumor only, compared to continuing gemcitabine, resulted in a small benefit: reduced local progression (32% versus 46%, p=0.03), borderline significant improvement in progression-free survival (9.9 months versus 8.4 months, p=0.06) with similar toxicity except increased G3-4 nausea (5.9% vs 0%, p=0.008). Thus, for LAPC, options include systemic treatment alone or the addition of chemoradiotherapy after chemotherapy. It may be that with better hematogenous disease control with more effective systemic treatment (Suker et al. 2016), the addition of RT may be more important in achieving local control.

Borderline Resectable Pancreatic Cancer

Neoadjuvant treatment potentially reduces the significant risks of positive margins and local and distant recurrence, and avoids futile surgery by identification of early development of metastatic disease (Toesca et al. 2018). Two small randomized phase II studies (Golcher et al. 2015; Jang et al. 2018) and a Phase III study (Versteijne et al. 2020) have shown that for BRPC, neoadjuvant chemoradiotherapy reduces the rate of positive margins and improves local control, disease-free survival, and overall survival (17.6 versus 13.2 months, p=0.029). The data does not however prove that RT is an essential component of the neoadjuvant treatment. Our approach for fit patients is to treat with neoadjuvant modified FOLFIRINOX 4–8 cycles, and if insufficient response then RT 45 Gy in 25 fractions (often with simultaneous integrated boost to 50 Gy to sites of threatened margins along vessels) with concurrent capecitabine 830 mg/m2 BD on RT days (Tempero et al. 2021) aiming to achieve resectability with negative margins.

Resected Pancreatic Cancer

Randomized trials regarding potential benefits of adjuvant RT are confounded by underpowering (Van Laethem et al. 2010) or antiquated toxic RT negatively impacting on adjuvant chemotherapy delivery and thus survival (Neoptolemos et al. 2004). Adjuvant chemotherapy improves survival and should be prioritized (Conroy et al. 2018). However, between ¼ and ½ of patients will develop loco-regional recurrence (Conroy et al. 2018, Jones et al. 2019), with associated morbidity such as pain, bleeding, or obstruction and with resulting survival being as poor as for patients that develop metastatic disease (Jones et al. 2019). This provides a rationale for adding adjuvant RT which reduces local recurrence (Van Laethem et al. 2010) and by extrapolation from neoadjuvant trials (Versteijne et al. 2020) may thereby improve overall survival. We recommend adjuvant chemotherapy for 4–6 months, re-stage, and if no distant disease offer selected patients adjuvant chemoradiotherapy to 45 Gy in 25 fractions (with simultaneous integrated boost to 50 Gy to sites of close margins along vessels) with concurrent capecitabine 830 mg/m2 BD on RT days (Tempero et al. 2021).

Stereotactic Body Radiation Therapy (SBRT)

SBRT is an RT technique that precisely applies high doses of hypofractionated RT to small volumes and has shown promising results for LAPC (Petrelli et al. 2017) and for BRPC (Mellon et al. 2015). The addition of SABR to chemotherapy did not improve outcomes in BRPC in the Alliance randomized phase II trial (Katz et al. 2021). For both BRPC and LAPC this approach is being tested in the MASTERPLAN randomized phase II trial (Oar et al. 2021).

Palliative Radiotherapy

Locally uncontrolled disease commonly causes symptoms including pain, bleeding, or obstruction (Tempero et al. 2021). Short courses of palliative radiotherapy utilizing schedules such as 8 Gy times 1–3 fractions (Ebrahimi et al. 2018) or 25 Gy in 5 fractions (Wang et al. 2018) usually achieve improvement in pain (66% and 79% respectively) and are relatively well tolerated with commonest toxicities being mild acute nausea (51% and 30%) and pain flare (33% and 21%). Palliative radiotherapy may also be used for symptomatic sites of metastatic disease (Tempero et al. 2021).

Palliative Medicine

Jessica AL Borbasi & Rebecca Strutt

Quality of life and timely referral to specialized Palliative Medicine is of paramount importance for patients with pancreatic cancer (Sohal et al. 2016). Nearly all patients with pancreatic cancer report pain, and of these the majority have moderate to severe pain (Lohse and Brothers 2020; Westermann et al. 2019). Pain is caused by perineural invasion of the coeliac plexus, tumor obstruction of the main pancreatic duct, bowel or gastric outlet obstruction, infiltrative or metastatic pain (liver and peritoneum), surgical pain, and ascites (Drewes et al. 2018; Lohse and Brothers 2020). The pain is nociceptive, somatic, neuropathic, and visceral in nature (Lohse and Brothers 2020), and inadequate pain management can interfere with quality of life impairing activity and emotions (Damm et al. 2020).

The initial management of pain should follow the guidelines of the World Health Organization (WHO) analgesic pain ladder with the use of regular paracetamol or non-steroidal anti-inflammatory agents – unless pre-existing conditions preclude their use (Drewes et al. 2018). Given the severity of pain many patients require opioids (Zylberberg et al. 2022). Clinician expertise can overcome common fears regarding the use of opioids, and neuropathic agents should also be considered such as gabapentinoids or duloxetine (Lee et al. 2021; Reid et al. 2008). Non-opioid options include radiotherapy and nerve blocks (Buwenge et al. 2018; Wang et al. 2018). The pancreas is innervated by the coeliac plexus; the pancreatic tail also has innervation from the splenic plexus (Bapat et al. 2011). Direct perineural invasion occurs in the majority of patients causing typical epigastric and back pain (Bapat et al. 2011). Neurolytic blocks are recommended for patients with uncontrolled pancreatic pain despite opioids or those experiencing unacceptable opioid side effects (Amr and Makharita, 2013; Drewes et al. 2018).

Coeliac Plexus Block (CPB) and Coeliac Plexus Neurolysis (CPN) are often used interchangeably but a block is a transient interruption of pain transmission, usually with a local anesthetic without causing permanent nerve damage, whereas neurolysis is generally considered to be permanent procedure (Sachdev and Gress 2018). Neurolysis can be achieved via chemical (alcohol or phenol) or thermal (radiofrequency ablation-RFA) techniques. CPN can be performed via surgical splanchnectomy, percutaneously (PQ)-CPN, or via an endoscopic ultrasound guide (EUS)-CPN. A meta-analysis showed that CPN improved analgesia and decreased opioid–induced adverse effects in comparison with conventional analgesic treatment (Mercadante et al. 2015). Regarding the method of neurolysis, a small randomized single blinded study showed that EUS-RFA provided more pain relief over EUS-CPN (chemical) and improved the quality of life for patients with pancreatic cancer (Bang et al. 2019). However, there is not enough evidence currently to recommend EUS-RFA over EUS-CPN. It is important not to indicate to patients that they will be able to stop opioids completely after CPN. The most common side effects are orthostatic hypotension and diarrhea, but complications are rare (Nagels et al. 2013). Patients with disease at the head of the pancreas are more likely to respond positively to CPN compared to patients with disease in the body or tail of the pancreas (Rykowski and Hilgier 2000). In addition patients with more locally advanced disease or metastatic disease are less likely to respond, possibly due to more pain mechanisms being involved (Rykowski and Hilgier 2000).

As such, there is good quality evidence demonstrating the analgesic efficacy of CPN but limited data regarding the technique of choice (Mercadante et al. 2015). However, CPN has not been shown to consistently improve quality of life, improve survival, or reduce opioid consumption (Nagels et al. 2013; Wong et al. 2004) . Nonetheless, interventional techniques such as CPN have been described as a fourth step in the WHO analgesic pain ladder; these procedures may be necessary for patients with severe pain (Pergolizzi and Raffa 2014). Most patients receive partial or complete symptomatic relief up until their death (Kawamata et al. 1996). Clinicians should refer to interventional radiologists or pain specialists to ascertain what procedures are available locally.

Pain is not the only burdensome symptom in this group who also suffer nausea, anorexia, depression, fatigue, dry mouth, cachexia, maldigestion, and other symptoms from pancreatic exocrine insufficiency (Labori et al. 2006). Palliative Medicine is well placed to address these physical burdens as well as patient's psychosocial and spiritual needs (WHO). Care extends to families including partners of patients with pancreatic cancer. Caregivers are known to carry a high psychological burden and have an increased risk of depression requiring medications (Dengsø et al. 2021).

Early palliative care results in fewer inappropriate admissions to the Intensive Care Unit (ICU) at the end of life and fewer presentations to the Emergency Department (ED). These patients tended to be female and older (Bevins et al. 2021). A Canadian study showed that provision of inpatient or outpatient Palliative Care was associated with a reduction in all four measures of aggressive care near death (chemotherapy, ICU admissions, multiple ED visits, and hospitalizations), compared to patients who did not receive Palliative Care. Also, as the frequency of Palliative Care consultations rose, the likelihood of inappropriate interventions fell (Jang et al. 2015). This supports referral at the time of diagnosis (Sohal et al. 2016).

Summary

Omali Pitiyarachchi & David Goldstein

Patients with pancreatic cancer have a poor prognosis and are often diagnosed late with advanced disease due to vague presenting symptoms. When a pancreatic tumor is suspected, prompt investigation is recommended to make a tissue diagnosis. Patients should be referred to a recognized sub-specialty MDT with the capability of managing patients with pancreatic tumors. Network MDTs can be used to include clinicians from more regional centers or centers without the subspecialty expertise, to provide multimodality therapy options for all patients.

Some patients may proceed straight to resection, but confirmation of malignancy is required for patients with metastatic disease, and for patients where neoadjuvant therapy is being considered. A dual phase contrast enhanced computed tomography is the preferred imaging modality to evaluate resectability, and should be performed within four weeks of diagnosis (**Imaging** section). Patients are categorized as having resectable, borderline resectable, locally advanced and metastatic disease depending on the extent of tumor spread, and the anatomic, biological, and conditional factors as outlined in the **Surgical** section of this chapter. The only chance of a cure is with surgical resection, so it is important to consider neoadjuvant therapy for patients with borderline resectable and locally advanced disease. As outlined in the **Systemic therapy** and **Radiation** sections, neoadjuvant therapy can convert patients with unresectable disease at diagnosis to potentially resectable. Consider enrolling patients into a clinical trial if possible.

The mainstay of systemic therapy is with chemotherapy, but in special cases such as patients with MSI-H/dMMR or NTRK gene fusions, more targeted treatment could be considered. All patients diagnosed with pancreatic cancer, but especially those with unresectable and metastatic disease, should be referred to **Palliative Care** early in the diagnosis. It is important to consider the burden on caregivers.

There have been some small gains in outcomes over the past few years and the impact of best practice adjuvant and neoadjuvant therapy is likely to lead to additional gains. However, it is still a very poor outcome cancer with an unacceptably high mortality to incidence ratio.

Key Take Home Messages

- Reliable, cost-effective early diagnosis, and screening protocols for high-risk individuals
- The role of novel circulating biomarkers such as circulating tumor DNA and tumor cells
- The identification of more active anti-tumor therapeutics
- Active stromal reprogramming techniques
- Reversing immune suppression

Areas for Further Research

1. Diagnostic, predictive, and prognostic biomarkers
2. Combined targeted and immunotherapy regimens
3. Improved very early detection surveillance programs

Trusted Websites for Further Reading

https://www.pancreaticcancer.org.uk
https://www.cancer.org/cancer/pancreatic-cancer.html

Key Action Points

- Staging using appropriate imaging techniques
- Incorporate staging laparoscopy where appropriate
- Obtain adequate tissue for diagnosis, especially if embarking on neoadjuvant therapy
- Discussion at MDT and review of operability using appropriate guidelines (Isaji et al. 2018)
- Consideration of neoadjuvant therapy
- Inclusion of suitable patients in clinical trials
- Consistent use of adjuvant therapy
- Early referral for supportive care
- Careful integration of translational and clinical research (which is the key to future success and improved outcomes)

Further Resources

- **Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology,** (https://jnccn.org/view/journals/jnccn/19/4/article-p439.xml)
- **Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up** (https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/pancreatic-cancer/eupdate-cancer-of-the-pancreas-treatment-recommendations)
- Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL. **International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017.** Pancreatology. 2018 Jan;18(1):2–11. doi: 10.1016/j.pan.2017.11.011. Epub 2017 Nov 22. PMID: 29191513.

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References

AIHW. (2021). *Australian Institute of Health and Welfare* [Online]. Available: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-data-commentaries/how-are-pancreatic-cancer-rates-changing (Accessed on 25th July 2023).

Amr, Y.M. and Makharita, M.Y. (2013). Comparative study between 2 protocols for management of severe pain in patients with unresectable pancreatic cancer: one-year follow-up. *Clin J Pain* 29: 807–813.

Azari, F.S., Vollmer, C.M., Jr., Roses, R.E. et al. (2020). A contemporary analysis of palliative procedures in aborted pancreatoduodenectomy: morbidity, mortality, and impact on future therapy. *Surgery* 168: 1026–1031.

Bailey, P., Chang, D.K., Nones, K. et al. (2016). Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 531: 47–52.

Bang, J.Y., Sutton, B., Hawes, R.H., and Varadarajulu, S. (2019). EUS-guided celiac ganglion radiofrequency ablation versus celiac plexus neurolysis for palliation of pain in pancreatic cancer: a randomized controlled trial (with videos). *Gastrointest Endosc* 89: 58–66.e3.

Bapat, A.A., Hostetter, G., Von Hoff, D.D., and Han, H. (2011). Perineural invasion and associated pain in pancreatic cancer. *Nat Rev Cancer* 11: 695–707.

Barbour, A.P., Samra, J.S., Haghighi, K.S. et al. (2020). The AGITG GAP study: a phase II study of perioperative gemcitabine and nab-paclitaxel for resectable pancreas cancer. *Ann Surg Oncol* 27: 2506–2515.

Baugh, K.A., Tran Cao, H.S., Van Buren, G., 2nd et al. (2019). Understaging of clinical stage I pancreatic cancer and the impact of multimodality therapy. *Surgery* 165: 307–314.

Beleù, A., Calabrese, A., Rizzo, G. et al. (2019). Preoperative imaging evaluation after downstaging of pancreatic ductal adenocarcinoma: a multi-center study. *Cancers* 11: 267.

Bevins, J., Bhulani, N., Goksu, S.Y. et al. (2021). Early palliative care is associated with reduced emergency department utilization in pancreatic cancer. *Am J Clin Oncol* 44: 181–186.

Bockhorn, M., Uzunoglu, F.G., Adham, M. et al. (2014). Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 155: 977–988.

Bonin, E.A. and Baron, T.H. (2011). Preoperative biliary stents in pancreatic cancer. *J Hepatobiliary Pancreat Sci* 18: 621–629.

Boone, B.A., Steve, J., Zenati, M.S. et al. (2014). Serum CA 19-9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. *Ann Surg Oncol*, 21, 4351–4358.

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer J Clin* 68: 394–424.

Bundred, J.R., Kamarajah, S.K., Hammond, J.S. et al. (2020). Prehabilitation prior to surgery for pancreatic cancer: a systematic review. *Pancreatology* 20: 1243–1250.

Burge, M.E., O'rourke, N., Cavallucci, D. et al. (2015). A prospective study of the impact of fluorodeoxyglucose positron emission tomography with concurrent non-contrast CT scanning on the management of operable pancreatic and peri-ampullary cancers. *HPB (Oxford)* 17: 624–631.

Burmeister, E.A., O'connell, D.L., Beesley, V.L. et al. (2015). Describing patterns of care in pancreatic cancer: a population-based study. *Pancreas* 44: 1259–1265.

Burris, H.A., 3rd, Moore, M.J., Andersen, J. et al. (1997). Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 15: 2403–2413.

Butturini, G., Stocken, D.D., Wente, M.N. et al. (2008). Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. *Arch Surg* 143: 75–83; discussion 83.

Buwenge, M., Macchia, G., Arcelli, A. et al. (2018). Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief. *J Pain Res* 11: 2169–2178.

Casciani, F., Bassi, C., and Vollmer, C.M., Jr. (2021). Decision points in pancreatoduodenectomy: insights from the contemporary experts on prevention, mitigation, and management of postoperative pancreatic fistula. *Surgery* 170: 889–909.

Catenacci, D.V., Junttila, M.R., Karrison, T. et al. (2015). Randomized phase Ib/II study of gemcitabine plus placebo or vismodegib, a hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. *J Clin Oncol* 33: 4284–4292.

Chaika, N.V., Gebregiworgis, T., Lewallen, M.E. et al. (2012). MUC1 mucin stabilizes and activates hypoxia-inducible factor 1 alpha to regulate metabolism in pancreatic cancer. *Proc Natl Acad Sci U S A* 109: 13787–13792.

Chauffert, B., Mornex, F., Bonnetain, F. et al. (2008). Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 19: 1592–1599.

Chen, J., Yang, R., Lu, Y. et al. (2012). Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol* 138: 1433–1441.

Cheng, X.B., Sato, N., Kohi, S., and Yamaguchi, K. (2013). Prognostic impact of hyaluronan and its regulators in pancreatic ductal adenocarcinoma. *PLoS One* 8: e80765.

Cheng, Z.-X., Wang, D.-W., Liu, T. et al. (2014). Effects of the HIF-1α and NF-κB loop on epithelial-mesenchymal transition and chemoresistance induced by hypoxia in pancreatic cancer cells. *Oncol Rep* 31: 1891–1898.

Chun, Y.S., Pawlik, T.M., and Vauthey, J.N. (2018). 8th edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. *Ann Surg Oncol* 25: 845–847.

Collisson, E.A., Sadanandam, A., Olson, P. et al. (2011). Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat Med* 17: 500–503.

Conroy, T., Desseigne, F., Ychou, M. et al. (2011). FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364: 1817–1825.

Conroy, T., Hammel, P., Hebbar, M. et al. (2018). FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 379: 2395–2406.

Croke, J.M. and El-Sayed, S. (2012). Multidisciplinary management of cancer patients: chasing a shadow or real value? An overview of the literature. *Curr Oncol (Toronto, Ont)* 19: e232–e238.

Da Costa, W.L., Jr, Tran Cao, H.S., and Massarweh, N.N. (2020). Neoadjuvant treatment for patients with localized pancreatic adenocarcinoma: are we there yet? *JAMA Oncol* 6: 1163–1164.

Damm, M., Weniger, M., Kölsch, A.K. et al. (2020). The quality of pain management in pancreatic cancer: a prospective multi-center study. *Pancreatology* 20: 1511–1518.

Dengsø, K.E., Thomsen, T., Andersen, E.W. et al. (2021). The psychological symptom burden in partners of pancreatic cancer patients: a population-based cohort study. *Support Care Cancer* 29: 6689–6699.

Ding, D., Javed, A.A., Cunningham, D. et al. (2021). Challenges of the current precision medicine approach for pancreatic cancer: a single institution experience between 2013 and 2017. *Cancer Lett* 497: 221–228.

Diop-Frimpong, B., Chauhan, V.P., Krane, S. et al. (2011). Losartan inhibits collagen I synthesis and improves the distribution and efficacy of nanotherapeutics in tumors. *Proc Natl Acad Sci U S A* 108: 2909–2914.

Doebele, R.C., Drilon, A., Paz-Ares, L. et al. (2020). Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 21: 271–282.

Drewes, A.M., Campbell, C.M., Ceyhan, G.O. et al. (2018). Pain in pancreatic ductal adenocarcinoma: a multidisciplinary, international guideline for optimized management. *Pancreatology* 18: 446–457.

Drilon, A., Laetsch, T.W., Kummar, S. et al. (2018). Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children. *N Engl J Med* 378: 731–739.

Ducreux, M., Cuhna, A.S., Caramella, C. et al. (2015). Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26: v56–v68.

Ebrahimi, G., Rasch, C.R.N., and Van Tienhoven, G. (2018). Pain relief after a short course of palliative radiotherapy in pancreatic cancer, the Academic Medical Center (AMC) experience. *Acta Oncol* 57: 697–700.

Elyada, E., Bolisetty, M., Laise, P. et al. (2019). Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. *Cancer Discov* 9: 1102–1123.

Erkan, M., Hausmann, S., Michalski, C.W. et al. (2012). The role of stroma in pancreatic cancer: diagnostic and therapeutic implications. *Nat Rev Gastroenterol Hepatol* 9: 454–467.

Erkan, M., Michalski, C.W., Rieder, S. et al. (2008). The activated stroma index is a novel and independent prognostic marker in pancreatic ductal adenocarcinoma. *Clin Gastroenterol Hepatol* 6: 1155–1161.

Farma, J.M., Santillan, A.A., Melis, M. et al. (2008). PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg Oncol* 15: 2465–2471.

Ferrone, C.R., Marchegiani, G., Hong, T.S. et al. (2015). Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 261: 12–17.

Gandy, R.C., Barbour, A.P., Samra, J. et al. (2016). Refining the care of patients with pancreatic cancer: the AGITG Pancreatic Cancer Workshop consensus. *Med J Aust* 204: 419–422.

Gemenetzis, G., Groot, V.P., Blair, A.B. et al. (2019). Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. *Ann Surg* 270: 340–347.

Ghaneh, P., Palmer, D.H., Cicconi, S. et al. (2020). ESPAC-5F: four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer. *J Clin Oncol* 38: 4505-4505.

Glimelius, B., Hoffman, K., Sjödén, P.O. et al. (1996). Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 7: 593–600.

Golan, T., Hammel, P., Reni, M. et al. (2019). Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med* 381: 317–327.

Golcher, H., Brunner, T.B., Witzigmann, H. et al. (2015). Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol* 191: 7–16.

Hackert, T., Sachsenmaier, M., Hinz, U. et al. (2016). Locally advanced pancreatic cancer: neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. *Ann Surg* 264: 457–463.

Hammel, P., Huguet, F., Van Laethem, J.L. et al. (2016). Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *Jama* 315: 1844–1853.

Hartwig, W., Vollmer, C.M., Fingerhut, A. et al. (2014). Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). *Surgery* 156: 1–14.

Hazel, J.J., Thirlwell, M.P., Huggins, M. et al. (1981). Multi-drug chemotherapy with and without radiation for carcinoma of the stomach and pancreas: a prospective randomized trial. *J Can Assoc Radiol* 32: 164–165.

Hidalgo, M. (2010). Pancreatic cancer. *N Engl J Med* 362: 1605–1617.

Hong, S.B., Lee, S.S., Kim, J.H. et al. (2018). Pancreatic cancer CT: prediction of resectability according to NCCN criteria. *Radiol*. 289 (3): 710–718. doi: 10.1148/radiol.2018180628.

Huber, M., Brehm, C.U., Gress, T.M. et al. (2020). The immune microenvironment in pancreatic cancer. *Int J Mol Sci* 21 (19): 7307. Published 2020 Oct 3. doi: 10.3390/ijms21197307.

Hwang, R.F., Moore, T.T., Hattersley, M.M. et al. (2012). Inhibition of the hedgehog pathway targets the tumor-associated stroma in pancreatic cancer. *Mol Cancer Res* 10: 1147–1157.

Iglesias-Garcia, J., Dominguez-Munoz, J.E., Abdulkader, I. et al. (2011). Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol* 106 (9): 1705–1710. doi: 10.1038/ajg.2011.119.

Isaji, S., Mizuno, S., Windsor, J.A. et al. (2018). International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology* 18: 2–11.

Jalil, R., Ahmed, M., Green, J.S., and Sevdalis, N. (2013). Factors that can make an impact on decision-making and decision implementation in cancer multidisciplinary teams: an interview study of the provider perspective. *Int J Surg* 11: 389–394.

Jang, J.Y., Han, Y., Lee, H. et al. (2018). Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. *Ann Surg* 268: 215–222.

Jang, R.W., Krzyzanowska, M.K., Zimmermann, C. et al. (2015). Palliative care and the aggressiveness of end-of-life care in patients with advanced pancreatic cancer. *J Natl Cancer Inst* 107 (3): dju424. Published 2015 Jan 20. doi: 10.1093/jnci/dju424.

Janssen, Q.P., Buettner, S., Suker, M. et al. (2019). Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. *J Natl Cancer Inst* 111: 782–794.

Jones, R.P., Psarelli, E.E., Jackson, R. et al. (2019). Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. *JAMA Surg* 154 (11): 1038–1048. doi: 10.1001/jamasurg.2019.3337.

Jones, W.E., Suh, W.W., Abdel-Wahab, M. et al., Expert Panel on Radiation, O. (2017). ACR appropriateness criteria® resectable pancreatic cancer. *Am J Clin Oncol* 40: 109–117.

Kamphorst, J.J., Nofal, M., Commisso, C. et al. (2015). Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein. *Cancer Res* 75: 544–553.

Karamitopoulou, E. (2019). Tumour microenvironment of pancreatic cancer: immune landscape is dictated by molecular and histopathological features. *Br J Cancer* 121: 5–14.

Katz, M.H., Fleming, J.B., Bhosale, P. et al. (2012). Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 118: 5749–5756.

Katz, M.H., Pisters, P.W., Evans, D.B. et al. (2008). Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 206: 833–846; discussion 846-8.

Katz, M.H.G., Shi, Q., Meyers, J.P. et al. (2021). Alliance A021501: preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. *J Clin Oncol* 39: 377-377.

Kawamata, M., Ishitani, K., Ishikawa, K. et al. (1996). Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain* 64: 597–602.

Khan, M.A., Grimm, I.S., Ali, B. et al. (2017). A meta-analysis of endoscopic ultrasound-fine-needle aspiration compared to endoscopic ultrasound-fine-needle biopsy: diagnostic yield and the value of onsite cytopathological assessment. *Endosc Int Open* 5: E363–e375.

Khorana, A.A., Mckernin, S.E., Berlin, J. et al. (2019). Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. *J Clin Oncol* 37: 2082–2088.

Kim, E.J., Sahai, V., Abel, E.V. et al. (2014). Pilot clinical trial of hedgehog pathway inhibitor GDC-0449 (vismodegib) in combination with gemcitabine in patients with metastatic pancreatic adenocarcinoma. *Clin Cancer Res* 20: 5937–5945.

Klaassen, D.J., Macintyre, J.M., Catton, G.E. et al. (1985). Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil–an Eastern Cooperative Oncology Group study. *J Clin Oncol* 3: 373–378.

Kokkinos, J., Jensen, A., Sharbeen, G. et al. (2021a). Does the microenvironment hold the hidden key for functional precision medicine in pancreatic cancer? *Cancers (Basel)* 13.

Kokkinos, J., Sharbeen, G., Haghighi, K.S. et al. (2021b). Ex vivo culture of intact human patient derived pancreatic tumour tissue. *Sci Rep* 11: 1944.

Kowalewski, A., Szylberg, Ł., Saganek, M. et al. (2018). Emerging strategies in BRCA-positive pancreatic cancer. *J Cancer Res Clin Oncol* 144: 1503–1507.

Kunzmann, V., Algül, H., Goekkurt, E. et al. (2019). Conversion rate in locally advanced pancreatic cancer (LAPC) after nab-paclitaxel/gemcitabine- or FOLFIRINOX-based induction chemotherapy (NEOLAP): final results of a multicenter randomised phase II AIO trial. *Ann Oncol* 30: v253.

Labori, K.J., Hjermstad, M.J., Wester, T. et al. (2006). Symptom profiles and palliative care in advanced pancreatic cancer: a prospective study. *Support Care Cancer* 14: 1126–1133.

Lakatos, G., Petranyi, A., Szűcs, A. et al. (2017). Efficacy and safety of FOLFIRINOX in locally advanced pancreatic cancer. a single center experience. *Pathol Oncol Res* 23: 753–759.

Lamb, B.W., Green, J.S., Benn, J. et al. (2013). Improving decision making in multidisciplinary tumor boards: prospective longitudinal evaluation of a multicomponent intervention for 1,421 patients. *J Am Coll Surg* 217: 412–420.

Lampert, E.J., Zimmer, A., Padget, M. et al. (2020). Combination of PARP inhibitor olaparib, and PD-L1 inhibitor durvalumab, in recurrent ovarian cancer: a proof-of-concept phase II study. *Clin Cancer Res* 26: 4268–4279.

Lee, K.G., Roy, V., Laszlo, M. et al. (2021). Symptom management in pancreatic cancer. *Curr Treat Options Oncol* 22: 8.

Li, J., Wientjes, M.G., and Au, J.L. (2010). Pancreatic cancer: pathobiology, treatment options, and drug delivery. *Aaps j* 12: 223–232.

Ligorio, M., Sil, S., Malagon-Lopez, J. et al. (2019). Stromal microenvironment shapes the intratumoral architecture of pancreatic cancer. *Cell* 178: 160–175.e27.

Loehrer, P.J., Sr., Feng, Y., Cardenes, H. et al. (2011). Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 29: 4105–4112.

Lohse, I. and Brothers, S.P. (2020). Pathogenesis and treatment of pancreatic cancer related pain. *Anticancer Res* 40: 1789–1796.

Luz, L.P., Al-Haddad, M.A., Sey, M.S.L., and Dewitt, J.M. (2014). Applications of endoscopic ultrasound in pancreatic cancer. *World J Gastroenterol* 20: 7808–7818.

Maharaj, A.D., Evans, S.M., Zalcberg, J.R. et al. (2021). Barriers and enablers to the implementation of multidisciplinary team meetings: a qualitative study using the theoretical domains framework. *BMJ Qual Saf* 30: 792–803.

Marabelle, A., Le, D.T., Ascierto, P.A. et al. (2020). Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol* 38 (1): 1–10. doi: 10.1200/JCO.19.02105.

Martinez-Useros, J., Li, W., Cabeza-Morales, M., and Garcia-Foncillas, J. (2017). Oxidative stress: a new target for pancreatic cancer prognosis and treatment. *J Clin Med* 6 (3): 29. Published 2017 Mar 9. doi: 10.3390/jcm6030029.

Mayo, S.C., Gilson, M.M., Herman, J.M. et al. (2012). Management of patients with pancreatic adenocarcinoma: national trends in patient selection, operative management, and use of adjuvant therapy. *J Am Coll Surg* 214: 33–45.

Mcisaac, D.I., Taljaard, M., Bryson, G.L. et al. (2020). Frailty as a predictor of death or new disability after surgery: a prospective cohort study. *Ann Surg* 271: 283–289.

Mellon, E.A., Hoffe, S.E., Springett, G.M. et al. (2015). Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol* 54: 979–985.

Mercadante, S., Klepstad, P., Kurita, G.P. et al. (2015). Sympathetic blocks for visceral cancer pain management: a systematic review and EAPC recommendations. *Crit Rev Oncol Hematol* 96: 577–583.

Miller, B.W., Morton, J.P., Pinese, M. et al. (2015). Targeting the LOX/hypoxia axis reverses many of the features that make pancreatic cancer deadly: inhibition of LOX abrogates metastasis and enhances drug efficacy. *EMBO Mol Med* 7: 1063–1076.

Moffitt, R.A., Marayati, R., Flate, E.L. et al. (2015). Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat Genet* 47: 1168–1178.

Motoi, F., Kosuge, T., Ueno, H. et al. (2019). Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol* 49: 190–194.

Motosugi, U., Ichikawa, T., Morisaka, H. et al. (2011). Detection of pancreatic carcinoma and liver metastases with gadoxetic acid–enhanced MR imaging: comparison with contrast-enhanced multi–detector row CT. *Radiol.* 260 (2): 446–453. doi: 10.1148/radiol.11103548.

Murakami, Y., Satoi, S., Motoi, F. et al. (2015). Portal or superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head carcinoma. *Br J Surg* 102: 837–846.

Nagels, W., Pease, N., Bekkering, G. et al. (2013). Celiac plexus neurolysis for abdominal cancer pain: a systematic review. *Pain Med* 14: 1140–1163.

(2004). N Engl J Med 350: 1200–1210. doi: 10.1056/NEJMoa032295.

Neoptolemos, J.P., Stocken, D.D., Friess, H., Bassi, C. et al. (2004). A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 350 (12): 1200–1210. doi: 10.1056/NEJMoa032295.

Neoptolemos, J.P., Palmer, D.H., Ghaneh, P. et al. (2017). Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 389: 1011–1024.

Neoptolemos, J.P., Palmer, D.H., Ghaneh, P. et al. (2020). ESPAC-4: a multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma: five year follow-up. *J Clin Oncol* 38: 4516–4516.

Norris, C.M. and Close, J.C.T. (2020). Prehabilitation for the frailty syndrome: improving outcomes for our most vulnerable patients. *Anesth Analg* 130: 1524–1533.

O'Reilly, E.M., Lee, J.W., Zalupski, M. et al. (2020). Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. *J Clin Oncol* 38: 1378–1388.

Oar, A., Lee, M., Le, H. et al. (2021). AGITG MASTERPLAN: a randomised phase II study of modified FOLFIRINOX alone or in combination with stereotactic body radiotherapy for patients with high-risk and locally advanced pancreatic cancer. *BMC Cancer* 21: 936.

Oettle, H., Neuhaus, P., Hochhaus, A. et al. (2013). Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *Jama* 310: 1473–1481.

Oettle, H., Post, S., Neuhaus, P. et al. (2007). Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancera randomized controlled trial. *JAMA* 297: 267–277.

Öhlund, D., Handly-Santana, A., Biffi, G. et al. (2017). Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. *J Exp Med* 214: 579–596.

Olive, K.P., Jacobetz, M.A., Davidson, C.J. et al. (2009a). Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 324: 1457–1461.

Olive, K.P., Jacobetz, M.A., Davidson, C.J. et al. (2009b). Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 324: 1457–1461.

Ouaïssi, M., Turrini, O., Hubert, C. et al. (2014). Vascular resection during radical resection of pancreatic adenocarcinomas: evolution over the past 15 years. *J Hepatobiliary Pancreat Sci* 21: 623–638.

Ozaki, H., Hiraoka, T., Mizumoto, R. et al. (1999). The prognostic significance of lymph node metastasis and intrapancreatic perineural invasion in pancreatic cancer after curative resection. *Surg Today* 29: 16–22.

Pan, M., Reid, M.A., Lowman, X.H. et al. (2016). Regional glutamine deficiency in tumours promotes dedifferentiation through inhibition of histone demethylation. *Nat Cell Biol* 18: 1090–1101.

Pan, X., Zhou, J., Xiao, Q. et al. (2021). Cancer-associated fibroblast heterogeneity is associated with organ-specific metastasis in pancreatic ductal adenocarcinoma. *J Hematol Oncol* 14: 184.

Pawlik, T.M., Laheru, D., Hruban, R.H. et al. (2008). Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. *Ann Surg Oncol* 15: 2081–2088.

Peng, J.S., Mino, J., Monteiro, R. et al. (2017). Diagnostic laparoscopy prior to neoadjuvant therapy in pancreatic cancer is high yield: an analysis of outcomes and costs. *J Gastrointest Surg* 21: 1420–1427.

Pergolizzi, J. and Raffa, R. (2014). The WHO pain ladder: do we need another step? *Pract Pain Manag* 14 (1).

Petersen, G.M. (2016). Familial pancreatic cancer. *Semin Oncol* 43: 548–553.

Petrelli, F., Comito, T., Ghidini, A. et al. (2017). Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. *Int J Radiat Oncol Biol Phys* 97: 313–322.

Phillips, P. (2012). Pancreatic stellate cells and fibrosis. In: *Pancreatic Cancer and Tumor Microenvironment* (ed. P.J. Grippo and H.G. Munshi). Trivandrum (India): Transworld Research Network Copyright © 2012, Transworld Research Network.

Pilarski, R. (2019). The role of BRCA testing in hereditary pancreatic and prostate cancer families. *Am Soc Clin Oncol EducBook* 39: 79–86.

Pishvaian, M.J., Blais, E.M., Brody, J.R. et al. (2020). Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. *Lancet Oncol* 21: 508–518.

Provenzano, P.P., Cuevas, C., Chang, A.E. et al. (2012). Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell* 21: 418–429.

Qayyum, A., Tamm, E.P., Kamel, I.R. et al. (2017). ACR appropriateness criteria(®) staging of pancreatic ductal adenocarcinoma. *J Am Coll Radiol* 14: S560–s569.

Qin, C., Yang, G., Yang, J. et al. (2020). Metabolism of pancreatic cancer: paving the way to better anticancer strategies. *Mol Cancer* 19: 50.

Rahib, L., Smith, B.D., Aizenberg, R. et al. (2014). Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 74: 2913–2921.

Ravikumar, R., Sabin, C., Abu Hilal, M. et al. (2014). Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. *J Am Coll Surg* 218: 401–411.

Reid, C.M., Gooberman-Hill, R., and Hanks, G.W. (2008). Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. *Ann Oncol* 19: 44–48.

Reni, M., Riess, H., O'Reilly, E. et al. (2019). An international, randomized, open-label, phase III trial of adjuvant nab-paclitaxel plus gemcitabine vs gemcitabine alone for surgically resected pancreatic adenocarcinoma (APACT): primary analysis and quality of life outcomes. *Ann Oncol* 30: iv126.

Rombouts, S.J., Walma, M.S., Vogel, J.A. et al. (2016). Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. *Ann Surg Oncol* 23: 4352–4360.

Rykowski, J.J. and Hilgier, M. (2000). Efficacy of neurolytic celiac plexus block in varying locations of pancreatic cancer: influence on pain relief. *Anesthesiology* 92: 347–354.

Sachdev, A.H. and Gress, F.G. (2018). Celiac plexus block and neurolysis: a review. *Gastrointest Endosc Clin N Am* 28: 579–586.

Seo, D.W., Sherman, S., Dua, K.S. et al. (2019). Covered and uncovered biliary metal stents provide similar relief of biliary obstruction during neoadjuvant therapy in pancreatic cancer: a randomized trial. *Gastrointest Endosc* 90: 602-612.e4.

Sharbeen, G., Mccarroll, J.A., Akerman, A. et al. (2021). Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma determine response to SLC7A11 inhibition. *Cancer Res* 81: 3461–3479.

Sharpe, S.M., Talamonti, M.S., Wang, C.E. et al. (2015). Early national experience with laparoscopic pancreaticoduodenectomy for ductal adenocarcinoma: a comparison of laparoscopic pancreaticoduodenectomy and open pancreaticoduodenectomy from the national cancer data base. *J Am Coll Surg* 221: 175–184.

Shrikhande, S.V., Barreto, S.G., Goel, M., and Arya, S. (2012). Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature. *HPB: Official J Int Hepato Pancreato Biliary Assoc* 14: 658–668.

Shukla, S.K., Purohit, V., Mehla, K. et al. (2017). MUC1 and HIF-1alpha signaling crosstalk induces anabolic glucose metabolism to impart gemcitabine resistance to pancreatic cancer. *Cancer Cell* 32: 71-87.e7.

Siegel, R.L., Miller, K.D., Fuchs, H.E., and Jemal, A. (2022). Cancer statistics, 2022. *CA: A Cancer J Clin* 72: 7–33.

Sohal, D.P., Mangu, P.B., Khorana, A.A. et al. (2016). Metastatic pancreatic cancer: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 34: 2784–2796.

Sohal, D.P.S., Duong, M., Ahmad, S.A. et al. (2021). Efficacy of perioperative chemotherapy for resectable pancreatic adenocarcinoma: a phase 2 randomized clinical trial. *JAMA Oncol* 7: 421–427.

Stairmand, J., Signal, L., Sarfati, D. et al. 2015. Consideration of comorbidity in treatment decision making in multidisciplinary cancer team meetings: a systematic review. *Ann Oncol*, 26, 1325–1332.

Stauffer, J.A., Coppola, A., Villacreses, D. et al. (2017). Laparoscopic versus open pancreaticoduodenectomy for pancreatic adenocarcinoma: long-term results at a single institution. *Surg Endosc* 31: 2233–2241.

Suker, M., Beumer, B.R., Sadot, E. et al. (2016). FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 17: 801–810.

Ta, R., O'Connor, D.B., Sulistijo, A. et al. (2019). The role of staging laparoscopy in resectable and borderline resectable pancreatic cancer: a systematic review and meta-analysis. *Dig Surg* 36: 251–260.

Tao, J., Yang, G., Zhou, W. et al. (2021). Targeting hypoxic tumor microenvironment in pancreatic cancer. *J Hematol Oncol* 14: 14.

Tas, F., Sen, F., Odabas, H. et al. (2013). Performance status of patients is the major prognostic factor at all stages of pancreatic cancer. *Int J Clin Oncol* 18: 839–846.

Taylor, C., Finnegan-John, J., and Green, J.S. (2014). "No decision about me without me" in the context of cancer multidisciplinary team meetings: a qualitative interview study. *BMC Health Serv Res* 14: 488.

Tempero, M.A., Malafa, M.P., Al-Hawary, M. et al. (2021). Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 19: 439–457.

Tempero, M.A., Malafa, M.P., Chiorean, E.G. et al. (2019). Pancreatic adenocarcinoma, version 1.2019. *J Natl Compr Canc Netw* 17: 202–210.

Toesca, D.A.S., Koong, A.J., Poultsides, G.A. et al. (2018). Management of borderline resectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 100: 1155–1174.

Tran Cao, H.S., Balachandran, A., Wang, H. et al. (2014). Radiographic tumor-vein interface as a predictor of intraoperative, pathologic, and oncologic outcomes in resectable and borderline resectable pancreatic cancer. *J Gastrointest Surg* 18: 269–278; discussion 278.

Tran Cao, H.S., Zhang, Q., Sada, Y.H. et al. (2017). Value of lymph node positivity in treatment planning for early stage pancreatic cancer. *Surgery* 162: 557–567.

Tréhoux, S., Duchêne, B., Jonckheere, N., and Van Seuningen, I. (2015). The MUC1 oncomucin regulates pancreatic cancer cell biological properties and chemoresistance. Implication of p42-44 MAPK, Akt, Bcl-2 and MMP13 pathways. *Biochem Biophys Res Commun* 456: 757–762.

Truty, M.J., Kendrick, M.L., Nagorney, D.M. et al. (2021). Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg* 273: 341–349.

Tzeng, C.W., Katz, M.H., Fleming, J.B. et al. (2014). Morbidity and mortality after pancreaticoduodenectomy in patients with borderline resectable type C clinical classification. *J Gastrointest Surg* 18: 146–155; discussion 155-6.

Valle, J.W., Palmer, D., Jackson, R. et al. (2014). Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol* 32: 504–512.

Van Cutsem, E., Tempero, M.A., Sigal, D. et al. (2020). Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. *J Clin Oncol* 38: 3185–3194.

Van Laethem, J.L., Hammel, P., Mornex, F. et al. (2010). Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 28 (29): 4450–4456. doi: 10.1200/JCO.2010.30.3446.

Versteijne, E., Dam, J.L.V., Suker, M. et al. (2022). Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: long-term results of the Dutch randomized PREOPANC trial. *J Clin Oncol* 40: 1220–1230.

Versteijne, E., Suker, M., Groothuis, K. et al. (2020). Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. *J Clin Oncol* 38: 1763–1773.

Versteijne, E., Vogel, J.A., Besselink, M.G. et al. (2018). Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg* 105: 946–958.

Von Hoff, D.D., Ervin, T., Arena, F.P. et al. (2013). Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 369: 1691–1703.

Vonlaufen, A., Joshi, S., Qu, C. et al. (2008). Pancreatic stellate cells: partners in crime with pancreatic cancer cells. *Cancer Res* 68: 2085–2093.

Waddell, N., Pajic, M., Patch, A.M. et al. (2015). Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 518: 495–501.

Walters, D.M., Lapar, D.J., De Lange, E.E. et al. (2011). Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging of pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 18: 2764–2771.

Wang, F., Gill, A.J., Neale, M. et al. (2014a). Adverse tumor biology associated with mesenterico-portal vein resection influences survival in patients with pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 21: 1937–1947.

Wang, W., Shpaner, A., Krishna, S.G. et al. (2013). Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. *Gastrointest Endosc* 78: 73–80.

Wang, X.Y., Yang, F., Jin, C., and Fu, D.L. (2014b). Utility of PET/CT in diagnosis, staging, assessment of resectability and metabolic response of pancreatic cancer. *World J Gastroenterol* 20: 15580–15589.

Wang, Y., Timotin, E., Zia, W. et al. (2018). Pain palliation using hypofractionated radiotherapy for unresectable pancreatic cancer. *J Med Imaging Radiat Sci* 49: 293–300.

Westermann, A., Matrisian, L.M., and Rahib, L. (2019). The need for improvement in the management of fatigue, depression and pain in pancreatic cancer. *J Clin Oncol* 37: 429-429.

Whatcott, C.J., Diep, C.H., Jiang, P. et al. (2015). Desmoplasia in primary tumors and metastatic lesions of pancreatic cancer. *Clin Cancer Res* 21: 3561–3568.

WHO. *Palliative care* [Online]. (2020). World Health Organization. Available: https://www.who.int/health-topics/palliative-care (accessed on 26th April 2022).

Wong, G.Y., Schroeder, D.R., Carns, P.E. et al. (2004). Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. *Jama* 291: 1092–1099.

Xia, B.T., Fu, B., Wang, J. et al. (2017). Does radiologic response correlate to pathologic response in patients undergoing neoadjuvant therapy for borderline resectable pancreatic malignancy? *J Surg Oncol* 115: 376–383.

Xu, Z., Vonlaufen, A., Phillips, P.A. et al. (2010). Role of pancreatic stellate cells in pancreatic cancer metastasis. *Am J Pathol* 177: 2585–2596.

Yamada, S., Fujii, T., Sugimoto, H. et al. (2013). Aggressive surgery for borderline resectable pancreatic cancer: evaluation of National Comprehensive Cancer Network guidelines. *pancreas* 42: 1004–1010.

Yamada, S., Shimada, M., Morine, Y. et al. (2021). Significance of frailty in prognosis after surgery in patients with pancreatic ductal adenocarcinoma. *World J Surg Oncol* 19: 94–94.

Yamada, S., Sugimoto, H., Kanazumi, N. et al. (2009). Prognostic factors for survival after extended pancreatectomy for pancreatic head cancer: influence of resection margin status on survival. *Pancreas* 38: 605–612.

Young, E.L., Thompson, B.A., Neklason, D.W. et al. (2018). Pancreatic cancer as a sentinel for hereditary cancer predisposition. *BMC Cancer* 18: 697.

Zamboni, G.A., Kruskal, J.B., Vollmer, C.M. et al. (2007). Pancreatic adenocarcinoma: value of multidetector CT angiography in preoperative evaluation. *Radiology* 245: 770–778.

Zhang, Y., Huang, J., Chen, M., and Jiao, L.R. (2012). Preoperative vascular evaluation with computed tomography and magnetic resonance imaging for pancreatic cancer: a meta-analysis. *Pancreatology* 12: 227–233.

Zhou, Y., Zhou, Q., Li, Z. et al. (2012). The impact of internal or external transanastomotic pancreatic duct stents following pancreaticojejunostomy. Which one is better? A meta-analysis. *J Gastrointest Surg* 16 (12): 2322–2335. doi: 10.1007/s11605-012-1987-2.

Zylberberg, H.M., Woodrell, C., Rustgi, S.D. et al. (2022). Opioid prescription is associated with increased survival in older adult patients with pancreatic cancer in the United States: a propensity score analysis. *JCO Oncol Pract* 0: OP.21.00488.

21 Management of Intrahepatic and Extrahepatic Cholangiocarcinoma

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Background

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Anatomical Classification

The current anatomical classification of cholangiocarcinoma (CCA) divides tumors into intrahepatic (iCCA; proximal to secondary biliary radicles; 10–20% of CCA), perihilar (pCCA; distal to secondary biliary radicles but proximal to cystic duct insertion; 50–60% of CCA) and distal (dCCA; below the cystic duct insertion; 20–30% of CCA). pCCA and dCCA are often grouped as extrahepatic CCA (eCCA). This classification has implications for presentation, diagnosis, management, and prognosis.

The Bismuth-Corlette classification (Bismuth and Corlette 1975) further classifies pCCA, describing lesions that are confined to the hepatic duct (I), confluence (II), confluence and right intrahepatic duct up to secondary biliary radicles (IIIA, see Figure 2), confluence and left intrahepatic duct up to secondary biliary radicles (IIIB) and multifocal (IV) (see Figure 1).

Presentation

The presentation of CCA often differs according to subtype. The most common presenting symptom of eCCA is painless jaundice. Associated symptoms may include pain, pruritis, fever, or constitutional symptoms (Alvaro et al. 2011) . In contrast, jaundice is less frequent in iCCA, with abdominal pain being the most common presenting symptom (DeOliveira et al. 2007). Importantly, 28–39% of iCCA subjects are asymptomatic at presentation with incidental abnormalities identified on laboratory testing or imaging.

Although most CCAs arise *de novo*, predisposing conditions exist. These relate to chronic biliary stasis and inflammation. Primary Sclerosing Cholangitis (PSC) in particular is relevant since as many as one in three patients ultimately succumb to CCA (Boonstra et al. 2013). In this setting CCA may present with jaundice or constitutional symptoms. Alternatively, CCA may be suspected in the setting of progressive liver function test deterioration, rising tumor markers (i.e. CA 19–9) or abnormal imaging as part of a screening program. Screening is common and improves survival (Ali et al. 2018). Choledochal cysts are another group susceptible to CCA development, with studies showing a risk of ranging between 0–17%, depending on the sampled population, and duration of follow up. Younger subjects are managed with prophylactic resectional surgery (Baison et al. 2019). Pyogenic cholangitis is a condition of intra-hepatic cholelithiasis that has been associated with a cumulative CCA incidence of approximately 5% over 5 years (M. Chen et al. 1993). In part this relates to an association between pyogenic cholangitis and endemic infestations with the liver fluke *Opisthorchis viverrini* and *Clonorchis sinensis* in East and South-East Asia (Banales et al. 2020).

Laboratory Testing

Serum bilirubin levels are often elevated, predominantly the conjugated fraction. Similarly, elevations of liver enzymes in a predominantly cholestatic pattern is typical including serum alkaline phosphatase and gamma glutamyl transferase levels. In general, levels of liver function tests are lower for iCCA. Similarly, in the setting of an extra-hepatic biliary stricture, higher serum bilirubin levels are more likely to suggest a malignant versus benign biliary etiology, with levels >100 µmmol/L having a sensitivity of 72% and specificity of 87% (Garcea et al.

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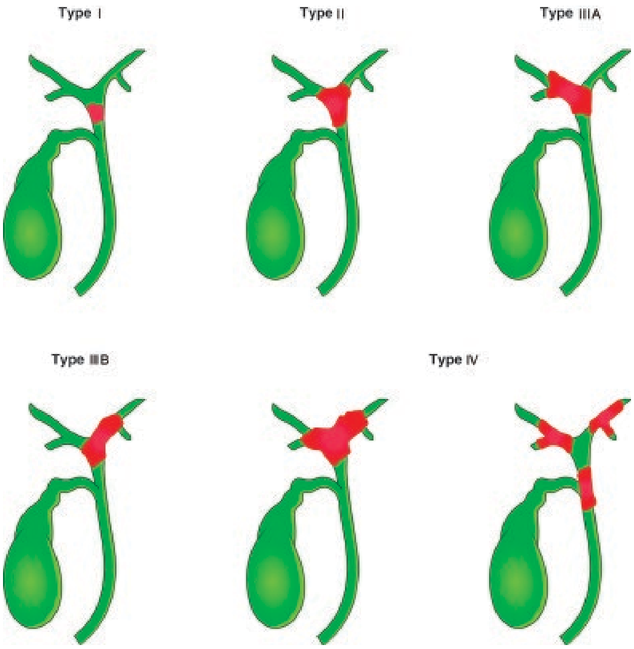

Figure 1 Cartoon of Bismuth Classification.

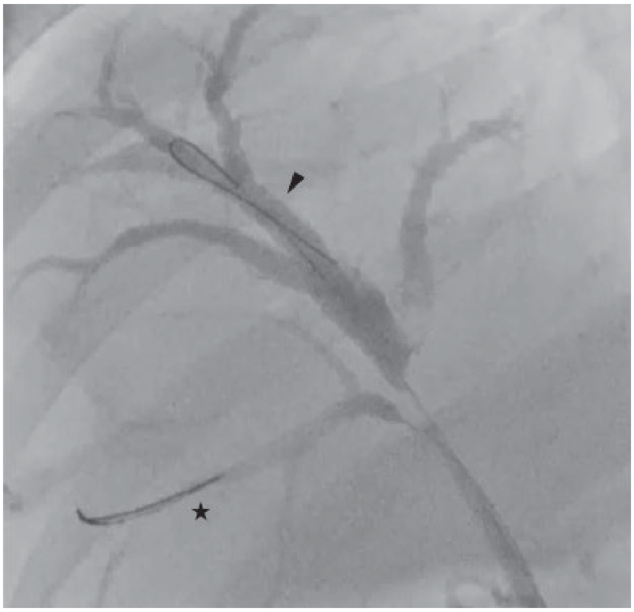

Figure 2 A likely Bismuth 3A stricture seen at ERCP; guidewires can be seen in the Right anterior (arrowhead) and posterior (star) sectoral ducts.

2011). Biliary obstruction may induce fat-soluble vitamin malabsorption, particularly vitamin K resulting in a coagulopathy which may be corrected with parenteral replacement.

The role of specific tumor markers being potentially elevated in CCA including carbohydrate antigen 19–9 (CA 19–9) are addressed in Chapter 17.

Differential Diagnosis

The differential diagnosis for CCA depends on the clinical presentation. A patient presenting with painless jaundice with imaging demonstrating a mass with biliary obstruction is likely to have an underlying malignancy, although IgG4-related disease may also present in this manner. In patients without a mass, the differential includes neoplastic and non-neoplastic causes including post-surgical (including transplant) or radiotherapy-induced strictures, chronic pancreatitis, PSC, IgG4 cholangiopathy and other rare causes.

Imaging and Staging

Oliver M. Fisher

Imaging Modalities for Staging Intra-hepatic and Perihilar Cholangiocarcinoma

High-quality multiplane, fine-slice computed tomography using IV-contrast arterial, portal-venous and delayed phases is the baseline examination to asses CCA extent. To further characterize the extent of ductal involvement, contrast-enhanced MRI with magnetic resonance cholangio-pancreatography (MRCP) is often employed as an alternative to more invasive endoscopic retrograde cholangiography (ERCP) or percutaneous transhepatic cholangiography (PTC). ERCP and PTC have the added benefit of providing improved biliary drainage and allow the facility to obtain cytological or biopsy sampling of detected lesions.

Given that the main differential for mass-forming iCCA is HCC, dynamic CT or MRI usually distinguish the two entities. Over 80% of iCCAs have characteristic CT contrast-behavior with progressive uptake during arterial and portal-venous and delayed phases, whereby HCC is typically characterized by arterial contrast uptake with washout during delayed phases (Rimola et al. 2009).

Whilst MRI may aid in satellite lesion detection, contrast-enhanced CT scans are most helpful for assessment of vascular involvement (Vilgrain 2008). PET-CT is helpful in larger (>1cm) mass-forming iCCA with a sensitivity and specificity >90% (Van Beers 2008). The principal role for PET is detection of nodal and distant metastases with sensitivity and specificity of 100% and 94%, respectively (Corvera et al. 2008). However, unfortunately for infiltrative CCA the sensitivity of PET is <20% (Van Beers 2008).

For pCCA CT has a reported accuracy of detecting portal vein involvement of >80% with identification of arterial involvement in >90%, which is superior to MRI (H. Y. Lee et al. 2006). Overall the accuracy of CT for determining resectability is 60–88%, however it's sensitivity for local lymph node involvement detection is only 54% (Aloia et al. 2007; H. Y. Lee et al. 2006; Tillich et al. 1998; Vilgrain 2008). CT scanning may underestimate the extent of proximal tumor extension (Blechacz et al. 2011). MRI findings are complementary to CT in pCCA, since its ability to assess tumor extent and resectability is similar to ERCP at 95% (Lopera et al. 2001; Masselli et al. 2008; Vogl et al. 2006). PET-CT is less helpful in staging p-CCA, with sensitivity and specificity <70% and poor lymph node detection rates (Kato et al. 2002; Kluge et al. 2001). Endoscopic ultrasound may be important in lymph node sampling (see advanced imaging).

Staging of intrahepatic Cholangiocarcinoma

iCCA is typically staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastases classification (Table 1) (Amin 2017). Herein, solitary tumors involving only the liver without evidence of vascular invasion are grouped into T1a if <5 cm or T1b if >5 cm in diameter. T2 is solitary vascular invasion or multifocality within the liver. T3 cancers invade through the visceral peritoneum not involving extrahepatic structures, and T4 cancers grow by direct extension into surrounding structures.

For accurate nodal staging, AJCC requires at least six lymph nodes to be sampled during resection allowing for accurate prognostication to select appropriate adjuvant treatment (Mazzaferro et al. 2020). Involvement of at least one regional node, renders patients N1. Extra-regional lymph nodes are regarded as distant metastases (M1). Thus, for all iCCA spread to para-aortic, coeliac, and pericaval lymph nodes are regarded as M1-disease. AJCC also list the following with worse survival: non-tumoral hepatic fibrosis, underlying PSC, and serum CA19.9 levels >200 U/ml. Other factors that may determine unresectability include locally advanced tumors affecting hepatic/inflow bilaterally, multiple intra-hepatic tumors, multiple satellite lesions, extensive perihepatic lymphadenopathy, the presence of portal hypertension and M1 disease (Table 2) (DeOliveira et al. 2007).

Table 1 TNM-staging/AJCC prognostic staging groups.

T-stage	N-stage	M-stage	AJCC stage group
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIB
Any T	Any N	M1	IV

Table 2 Criteria indicating potential unresectability in pCCA[1].

1	Medical contraindications to surgery
2	Advanced cirrhosis/portal hypertension
3	Inadequate future liver remnant
4	Bilateral second-order biliary radical involvement
5	Bilateral hepatic arterial and/or portal venous involvement
6	Main portal vein involvement or encasement (unless suitable for resection)
7	Lobar atrophy with contralateral portal venous or second-order biliary radical involvement
8	Unilateral second-order biliary radical involvement with contralateral venous/arterial encasement/occlusion
9	N2 nodal involvement
10	Distant metastases

[1] Adapted from Jarnagin et al. (Jarnagin et al. 2001).

Staging of Perihilar Cholangiocarcinoma

The two most widely applied validated pCCA staging systems are the Bismuth-Corlette classification (Figure 1) and AJCC TNM staging system. The Bismuth-Corlette system implies surgical resectability, but correlates poorly with patient outcomes (Table X). Whilst the 8th AJCC staging correlates with patient outcomes, it is a pathology driven classification that does not predict surgical resectability and the ability to achieve a negative margin, which remains the main stage-independent driver of patient outcomes. The AJCC staging however informs postoperative risk stratification and adjuvant treatment selection. Earlier T-stages are still based on depth of penetration while later T-stages include vascular involvement given that these aspects of perihilar cholangiocarcinoma heavily influence outcomes. T3 cancers are those that invade ipsilateral portal venous or hepatic arterial branches. T4 cancers invade the main portal vein, or its branches bilaterally or, the common hepatic artery or, unilateral second order biliary radicals with contralateral portal venous or hepatic arterial involvement. The extent of lymph node involvement is inversely associated with patient survival (Aoba et al. 2013). Therefore, N0 disease reflects no nodal involvement, N1 1–3 and N2 >3 positive lymph nodes (AJCC). Local lymph nodes are classified as regional conversely, those distant to the hepato-duodenal ligament represent metastatic disease. Importantly, N2 disease now indicates stage IVa, and surgery is usually contraindicated due to poor survival.

Advanced Imaging and Diagnostic Tissue Acquisition

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Tissue diagnosis is the only way to definitively diagnose CCA. In the setting of potentially resectable iCCA, cross-sectional imaging findings may be enough for a putative diagnosis to be made, without necessitating biopsy. Percutaneous ultrasound or CT-guided biopsy may be undertaken, particularly in subjects not considered suitable for surgical resection. There is a risk of tumor seeding (Heimbach et al. 2011) meaning the patient's ultimate therapeutic goals need to be carefully considered. Specific histological characteristics of CCA are addressed in Chapter 15, of note, histological distinction between iCCA and metastatic adenocarcinoma may be difficult thereby necessitating further imaging or endoscopy.

In contrast to iCCA, tissue diagnosis of dCCA and pCCA is important and notoriously challenging. In the past surgery was often undertaken in these situations without preceding tissue confirmation, however this resulted in a substantial rate of resections, for benign disease, unacceptable for procedures which entail significant morbidity and mortality (Scheuermann et al. 2016). Recently, considerable attention has been paid to advanced means of interpreting tissue, with multiple nucleic acid-based tests appearing to improve diagnostic accuracy. These techniques are further addressed in Chapter 17. Moreover, tissue diagnosis is required before commencing either chemotherapy or radiotherapy. Advanced imaging and tissue acquisition can be performed using the following techniques:

- Endoscopic Retrograde Cholangiopancreatography (ERCP) allows both management of biliary obstruction and tissue sampling. ERCP obtains detailed images of the biliary tree, but with improvements in non-invasive biliary imaging, its main role is tissue acquisition and biliary drainage. Cytological specimens can be obtained from brushings of biliary strictures and histological specimens may also be obtained under ERCP guidance. Similar techniques can be employed during percutaneous transhepatic approaches to biliary strictures. In these settings cytological specimens and pathology each have specificities over 95% for CCA, but sensitivities of only between 20–70% (Yoon et al. 2022). With this poor sensitivity, often multiple attempts at tissue acquisition via different modalities are required to obtain a firm diagnosis.
- Endoscopic ultrasound (EUS) – EUS allows high resolution views of the biliary tree from the adjacent duodenum (Figure 3). In the setting of eCCA, visualization of a mass or bile duct wall thickening are usually identified. Under ultrasound guidance, a needle can be passed through the echoendoscope to puncture the area of concern. It is possible to collect either cytological or core specimens for histological assessment. The sensitivity of EUS fine needle aspiration/biopsy (FNA/FNB) is 43–89%, with specificities over 95% (Khashab et al. 2012). Several analyses have stratified the accuracy of EUS-guided tissue acquisition for proximal versus distal biliary lesions, with increased sensitivities noted for distal lesions (Raine et al. 2020). There is a risk of seeding tumor along the needle tract during tissue sampling which is a particular concern for pCCA, where peritoneal seeding is a risk (Heimbach et al. 2011), thereby limiting the utility of EUS for this indication. EUS can also be used for CCA staging, allowing assessment of local vascular invasion and lymph node metastases (Gleeson et al. 2008).
- Cholangioscopy – modern digital single-operator cholangioscopy is performed by passing a cholangioscope through the instrument channel of a duodenoscope during ERCP. This allows direct visualization of the biliary mucosa and characterization of biliary strictures and masses (Figure 4). The cholangioscope has an instrument channel allowing passage of small caliber biopsy forceps to enable targeted

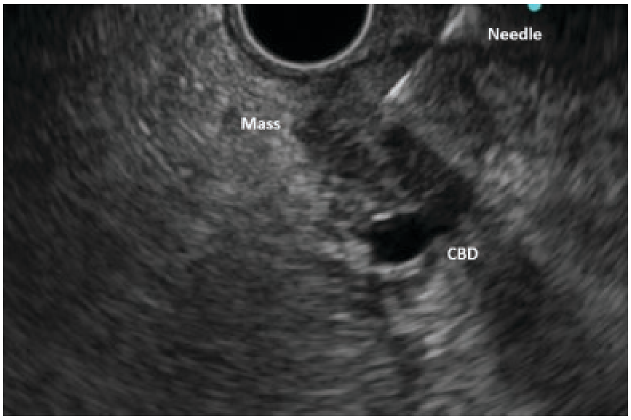

Figure 3 EUS FNA of an eccentric wall thickening of the distal bile duct; CBD – common bile duct.

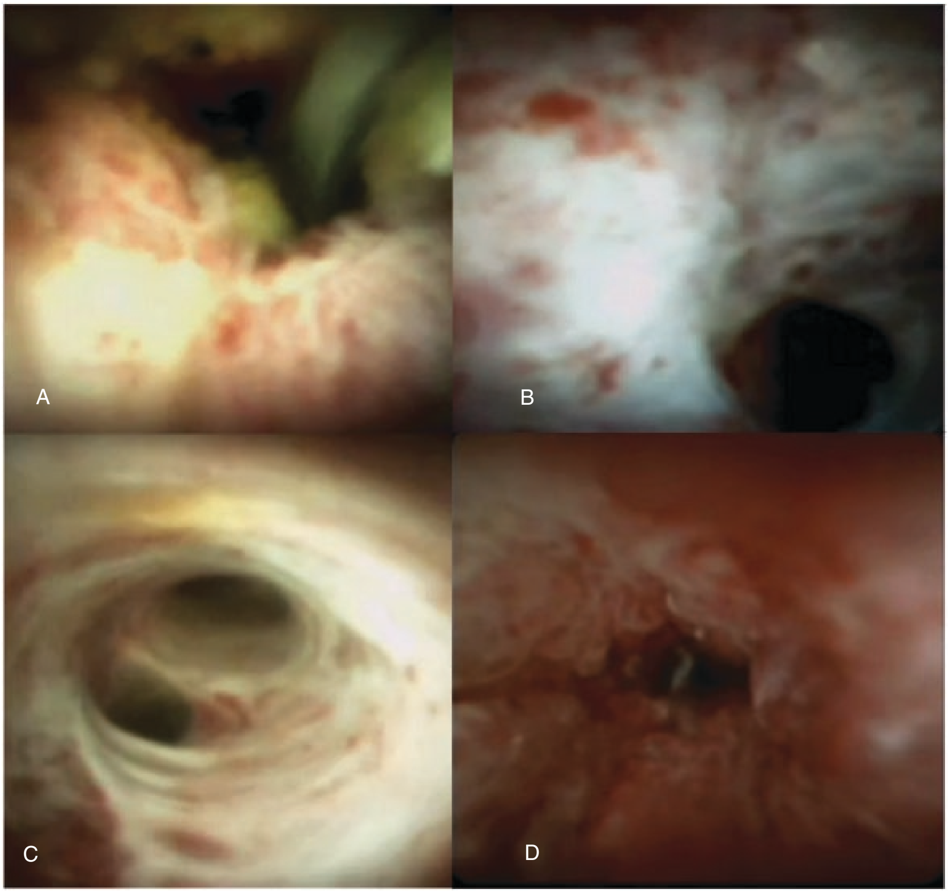

Figure 4 Biliary strictures seen at cholangioscopy. A & B – benign appearing; C & D – malignant appearing.

biopsies of biliary strictures. A recent meta-analysis reported the sensitivity of cholangioscopic-guided biopsies at 74% in this difficult cohort of indeterminate biliary strictures. Several other studies have assessed the endoscopist's, "visual impression" of indeterminate biliary strictures compared with the final diagnosis suggesting sensitivities ranging from 85–95% (Wen et al. 2020; Reynauld et al. 2021), though when blinded to other factors these sensitivities was reduced (Stassen et al. 2021) (Figure 5).

- Less common techniques: include Intra-ductal ultrasound (Krishna et al. 2007; Heinzow 2014; L. Chen et al. 2016), confocal laser endomicroscopy (CLE) (Slivka et al. 2015) and optical coherence tomography (OCT) (Arvanitakis et al. 2009). These techniques are not in widespread use but may have a role in expert centers.

Key Take Home Messages

1 The classic presentation of CCA is painless jaundice, but pain, pruritis, or fever also occurs; iCCA may present with either pain, abnormal LFTS or cross-sectional imaging

2 Laboratory and imaging features may be characteristic, but lack specificity in diagnosing CCA

3 Definitive, tissue diagnosis of eCCA may be challenging and includes use of ERCP, EUS and cholangioscopy

Surgery and Transplantation

Ngee-Soon Lau & Carlo Pulitano

Perihilar Cholangiocarcinoma

Surgery represents the only chance at cure for patients with pCCA (Cillo et al. 2019; Lauterio et al. 2021). The goal of surgery is R0 resection with clear margins, preservation of critical vascular structures, and adequate future liver remnant. This requires careful preoperative management to optimize biliary drainage and future liver remnant, and a considered approach

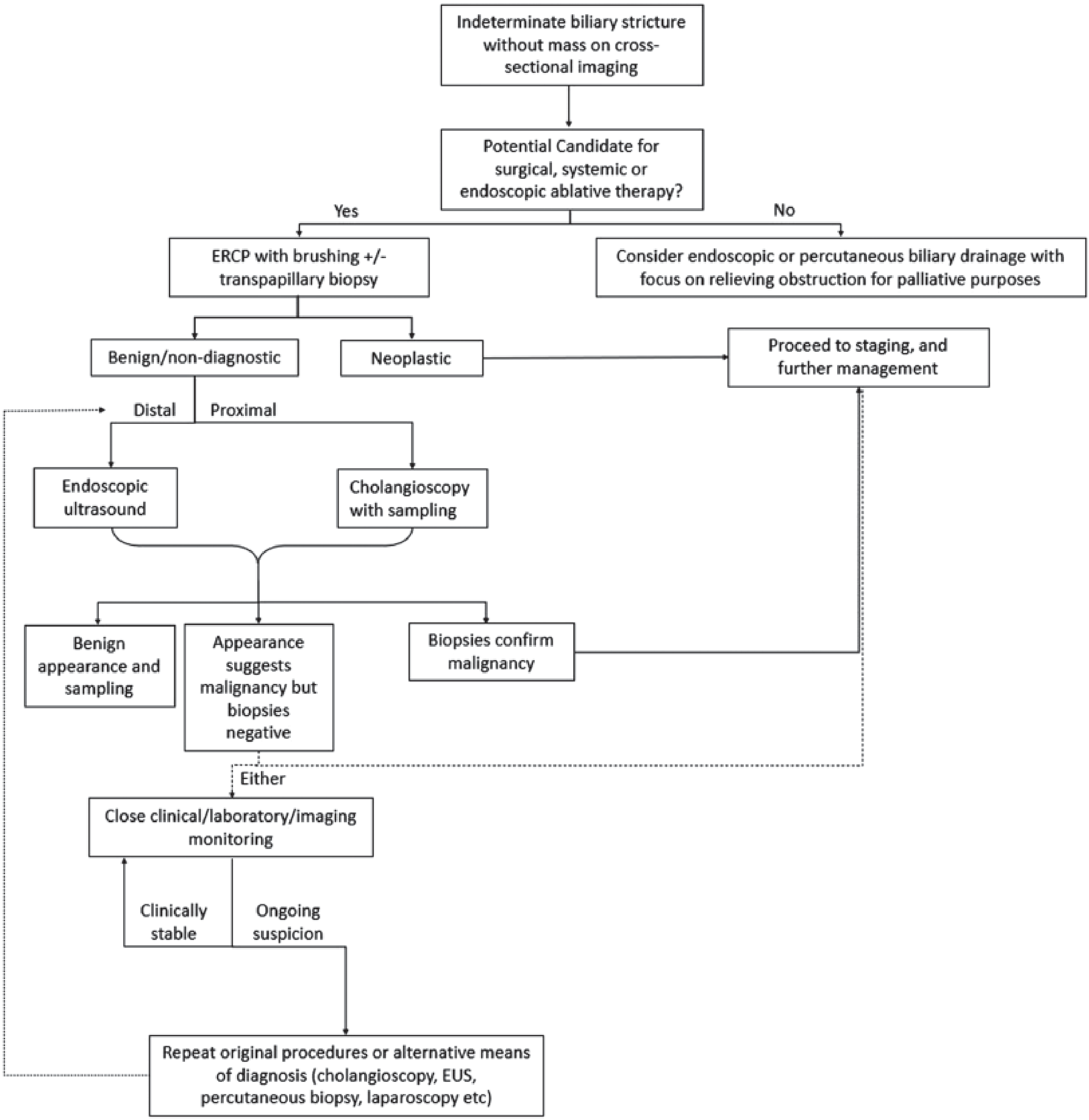
Indeterminate biliary stricture without mass on cross-sectional imaging
Potential Candidate for surgical, systemic or endoscopic ablative therapy?
Yes
No
ERCP with brushing +/- transpapillary biopsy
Consider endoscopic or percutaneous biliary drainage with focus on relieving obstruction for palliative purposes
Benign/non-diagnostic
Neoplastic
Proceed to staging, and further management
Distal
Proximal
Endoscopic ultrasound
Cholangioscopy with sampling
Benign appearance and sampling
Appearance suggests malignancy but biopsies negative
Biopsies confirm malignancy
Either
Close clinical/laboratory/imaging monitoring
Clinically stable
Ongoing suspicion
Repeat original procedures or alternative means of diagnosis (cholangioscopy, EUS, percutaneous biopsy, laparoscopy etc)

Figure 5 Approach to the diagnosis of indeterminate biliary strictures.

to resection with selected use of aggressive approaches such as extended liver resection and liver transplantation.

Preoperative Considerations

Preoperative Biliary Decompression

PCCA commonly presents with obstructive jaundice which is associated with a proinflammatory state which impairs the regenerative capacity of the liver (Kimmings et al. 1995; Krähenbühl et al. 1998). For this reason, preoperative biliary decompression is required in patients with cholangitis and those with a planned extensive resection or small future liver remnant requiring portal vein embolization (Farges et al. 2013; Iacono et al. 2013; Kennedy et al. 2009; Ribero et al. 2016; Su et al. 1996). Preoperative biliary decompression is associated with an increased risk of cholangitis, observed in both retrospective studies of pCCA (Ferrero et al. 2009; Hochwald et al. 1999), and a randomized controlled trial of patients with obstructive jaundice due to pancreatic cancer (van der Gaag et al. 2010). Therefore, preoperative biliary decompression should be used selectively in patients presenting with cholangitis or a serum bilirubin >4 mg/dL (68 umol/L) or a future liver remnant of <40% (Cillo et al. 2019).

The methods of achieving biliary decompression are either percutaneous or endoscopic biliary stenting. At meta-analysis, a percutaneous approach resulted in less pancreatitis, cholangitis, or failure than an endoscopic approach without significant differences in postoperative complications or survival (Al Mahjoub et al., 2017; Hameed et al. 2016). However, a percutaneous approach has the additional risk of tumor seeding (Wang et al. 2019).

Approach to Resection

Type of Resection

The type of hepatectomy performed depends on the extent of tumor invasion within the biliary tree and surrounding inflow vascular structures. Typically, to achieve adequate margins, patients require a right or left hemi-hepatectomy with resection of the bile duct (Nagino et al. 2013; Tran et al. 2019). If the degree of biliary invasion involves both right and left hepatic ducts (Bismuth IV), a right or left trisectionectomy is usually required often with reconstruction of multiple segmental ducts (Nagino et al. 2021; Neuhaus et al. 2012). A bile duct resection alone without hepatectomy is occasionally possible for cancers arising below the confluence of the hepatic ducts (Bismuth I), but this has been associated with a lower rate of R0 resection, lower nodal yield and a lower five-year survival (30% vs 50%) compared to resection of bile duct and liver en-bloc (de Jong et al. 2012; Lim et al. 2013). Resection of the caudate lobe with the hemi-hepatectomy or trisectionectomy is preferred because perihilar cholangiocarcinoma commonly extends into the caudate lobe either directly or through small biliary branches from the confluence of the hepatic ducts (Nimura et al. 1990).

Margins

Achieving an R0 resection is important for optimal postoperative outcomes and is therefore the surgical goal (Tang et al. 2018; Xiang et al. 2015). This can be challenging because CCA often spreads along the bile duct (Sakamoto et al. 1998). Moreover, intraoperative diagnosis of an R1 resection through frozen section may also be difficult (Mantel et al. 2016; Xiang et al. 2015).

Future Liver Remnant

To achieve an adequate resection in pCCA an extended hepatectomy is often required. This may place patients at risk of liver failure due to an inadequate future liver remnant. In pCCA portal vein embolization has also been used with good postoperative outcomes to improve the safety of liver resection when future liver remnant is <40% (Ebata et al. 2012; Glantzounis et al. 2017). Another strategy is the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure which facilitates rapid hypertrophy over a short period of time (Schnitzbauer et al. 2012). However, in pCCA outcomes after ALPPS are inferior to standard extended resections making portal vein embolization the preferred technique (Olthof et al. 2017).

Lymphadenectomy

Dissection of the regional nodes in the porta hepatitis including the hepatoduodenal lymph node is recommended (NCCN 2021). Lymphadenectomy was not associated with survival benefit, but overall lymph node status was an important prognostic indicator for long-term survival (Liang et al. 2021). Excision of >5 lymph nodes improves lymph node staging and prognostication (Liang et al. 2021).

Vascular Resection

Resection of the portal vein to improve the rate of R0 resection in pCCA has been widely practiced (de Jong et al. 2012; Neuhaus et al. 1999). More recently, portal vein resection when combined with a hepatectomy and bile duct resection improves long-term survival in selected patients (Abbas and Sandroussi 2013; de Jong et al. 2012). The benefits for resection of the hepatic artery in pCCA are less clear since although this improves R0 resection rates in advanced disease, survival is unchanged (Abbas and Sandroussi 2013; Y. M. Li et al. 2022).

Minimally Invasive Surgery

Advances in technology and increasing experience with minimally invasive surgery have increased enthusiasm for this approach for pCCA resections. The perceived benefits of less pain, shorter length of stay and precise, magnified visualization make this approach attractive (Hu et al. 2019; Ratti et al. 2020b). In a series of 16 laparoscopic resections, a minimally invasive approach resulted in a shorter length of stay and less blood loss than an open approach with similar rates of R0 resection (Ratti et al. 2020a). Another group have utilised a robotic-assisted approach to perform 48 pCCA resections and reported a 10% rate of major morbidity with no mortalities and an R0 resection in 73% of patients (J. Li et al. 2020b). All series to date however are limited by small numbers and therefore, this approach should only be performed at expert centers in selected patients (Hu et al. 2019).

Outcomes after Resection

Despite advances in resection for pCCA, long-term outcomes remain poor. Reported rates of mortality are 1–14% and the overall 5-year survival is 17–44% (Table 3).

Liver Transplantation

Using liver transplantation to treat pCCA has a number of advantages. Firstly, it overcomes challenges associated with attempting R0 resection by removing the liver and bile duct en-bloc permitting resection of tumors previously considered unresectable. Secondly, it avoids concerns about postoperative liver failure due to inadequate future liver remnant. Finally, it treats any underlying predisposing conditions such as cirrhosis or primary sclerosing cholangitis (Cillo et al. 2019; Lauterio et al., 2021). However, this impacts on transplant waiting lists therefore, due to donor shortages and historically poor outcomes after transplant for pCCA, uptake is limited (Acher et al. 2021).

Development of the Mayo Clinic Protocol in 1993 demonstrated encouraging results with 82% 5-year survival in a 24 patient cohort (Heimbach et al. 2004; Rosen et al. 2010). This protocol includes patients with unresectable disease and tumors <3 cm without evidence of metastases and involves neoadjuvant external beam radiation therapy, brachytherapy, chemotherapy and then surgical exploration and liver transplantation (Figure 6) (Rosen et al. 2010). Using protocol variations, several centers have reported similar results with 5-year overall survival 50–60% (Darwish Murad et al. 2012; Ethun

Table 3 Selected studies reporting outcomes after liver resection for pCCA.

Article, location	Study period, type	Number of patients	Morbidity <90 days	Mortality <90 days	5-year survival
Farges et al. (2013) Europe	1997–2008 Multi-center	366	69%	11%	-
Nagino et al. (2013) Japan	1977–2010 Single-center	574	57%	4%	33%
Yu et al. (2014) China	1998–2010 Single-center	238	18%	1%	17%
Furusawa et al. (2014) Japan	1990–2012 Single-center	144	73%	1%	Early period: 33% Late period: 35%
Tran et al. (2019) USA	2000–2015 Multi-center	257	58%	6%	19%
Franken et al. (2021) Netherlands	2000–2018 Single-center	178	77%	14%	Left resection: 44% Right resection: 38%
Nagino et al. (2021) Japan	2001–2018 Single-center	787	-	2%	Left resection: 39% Right resection: 42%

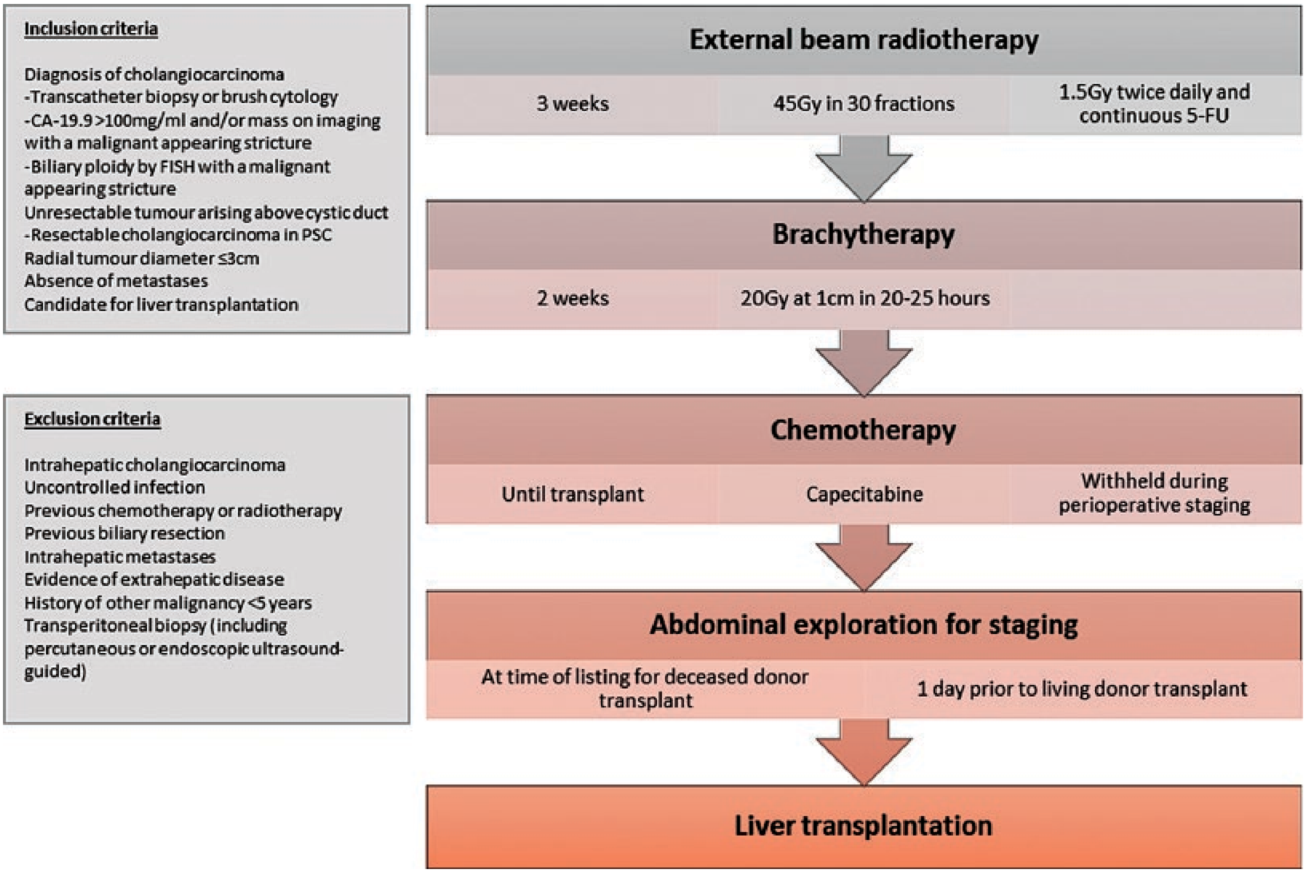
Inclusion criteria
Diagnosis of cholangiocarcinoma
-Transcatheter biopsy or brush cytology
-CA-19.9 >100mg/ml and/or mass on imaging with a malignant appearing stricture
-Biliary ploidy by FISH with a malignant appearing stricture
Unresectable tumour arising above cystic duct
-Resectable cholangiocarcinoma in PSC
Radial tumour diameter ≤3cm
Absence of metastases
Candidate for liver transplantation
Exclusion criteria
Intrahepatic cholangiocarcinoma
Uncontrolled infection
Previous chemotherapy or radiotherapy
Previous biliary resection
Intrahepatic metastases
Evidence of extrahepatic disease
History of other malignancy <5 years
Transperitoneal biopsy (including percutaneous or endoscopic ultrasound-guided)
External beam radiotherapy
3 weeks
45Gy in 30 fractions
1.5Gy twice daily and continuous 5-FU
Brachytherapy
2 weeks
20Gy at 1cm in 20-25 hours
Chemotherapy
Until transplant
Capecitabine
Withheld during perioperative staging
Abdominal exploration for staging
At time of listing for deceased donor transplant
1 day prior to living donor transplant
Liver transplantation

Figure 6 Mayo Clinic Protocol for neoadjuvant treatment followed by liver transplantation for pCCA. *Adapted from Rosen et al. (2010).*

et al. 2018; Tan et al. 2020; Zaborowski et al. 2020). A multicenter study of patients with "unresectable" disease undergoing liver transplantation found improved overall survival compared to patients undergoing resection for "resectable" disease (5-year survival 64% vs 18%) (Ethun et al. 2018). Debate continues about how to prioritize and select patients with p-CCA for transplantation with some centers utilizing living donation liver transplantation with comparable results (Tan et al. 2020).

Key Take Home Messages

1. Surgery is the only curative treatment for perihilar cholangiocarcinoma
2. Preoperative biliary drainage is preferred in patients presenting with cholangitis, a bilirubin >4 mg/dL (68 umol/L) or a future liver remnant of <40%
3. Portal vein embolization should be considered when the future liver remnant is <40%
4. Resection should include caudate lobectomy, lymphadenectomy and vascular resection if required
5. Liver transplantation can be considered in highly selected patients after neoadjuvant treatment using the Mayo Clinic Protocol (or similar)

A treatment algorithm for perihilar cholangiocarinoma is outlined in Figure 7.

Intrahepatic Cholangiocarcinoma

Overall Surgical Approach

Intrahepatic cholangiocarcinoma is an aggressive malignancy and although surgery is the only curative treatment, overall survival continues to be poor. The goal of surgery is an R0 resection with adequate future liver remnant but, due to late presentation and rapid progression, most are unresectable at diagnosis (Bridgewater et al. 2014; Lauterio et al. 2021; Mazzaferro et al. 2020). With recent advances and a more aggressive surgical approach, extended liver resections with vascular resection and reconstruction is an option in selected patients. (Lauterio et al. 2021; Mazzaferro et al. 2020). Liver transplantation remains experimental with encouraging results in small trials (Mazzaferro et al. 2020).

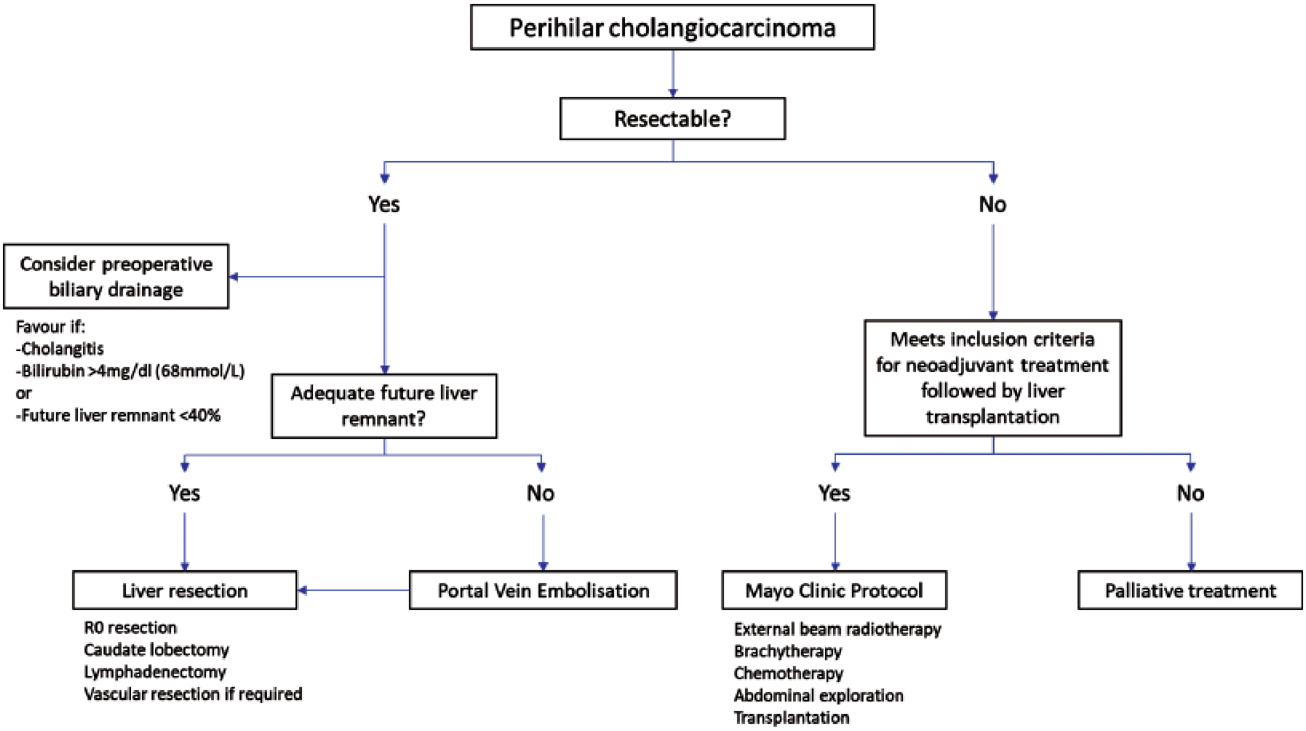
Perihilar cholangiocarcinoma
Resectable?
Yes
No
Consider preoperative biliary drainage
Favour if:
-Cholangitis
-Bilirubin >4mg/dl (68mmol/L)
or
-Future liver remnant <40%
Adequate future liver remnant?
Meets inclusion criteria for neoadjuvant treatment followed by liver transplantation
Yes
No
Yes
No
Liver resection
Portal Vein Embolisation
Mayo Clinic Protocol
Palliative treatment
R0 resection
Caudate lobectomy
Lymphadenectomy
Vascular resection if required
External beam radiotherapy
Brachytherapy
Chemotherapy
Abdominal exploration
Transplantation

Figure 7 Perihilar cholangiocarcinoma treatment algorithm.

Approach to Resection

Type of Resection

For small or peripheral tumors, an anatomical or non-anatomical/parenchymal sparing approach can be used; anatomical resections result in improved survival and lower recurrence rates (Si et al. 2019). Most patients have advanced disease at diagnosis and require a hemi-hepatectomy or extended hepatectomy (de Jong et al. 2011; Endo et al. 2008). Involvement of the biliary tree with biliary obstruction occurs occasionally requiring en-bloc resection and reconstruction (Endo et al. 2008; Mazzaferro et al. 2020). Preoperative biliary drainage again may be required (Cillo et al. 2019; Mazzaferro et al. 2020). Resection and reconstruction of the inferior biliary vena cava or portal vein may be performed in selected patients to achieve an R0 resection, with comparable outcomes (Alikhanov et al. 2021; Conci et al. 2020).

Margins

Although an R0 resection is ideal, there is conflicting evidence about its role as a predictor for survival and long-term recurrence (Farges et al. 2011; Murakami et al. 2011; Ribero et al. 2012). Lymph node status appears a more important prognostic marker (Hewitt et al. 2022; Lauterio et al., 2021). Notably, in a multicenter study of 212 patients, those with nodal metastases had similar outcomes irrespective of R1 or R0 resection status, while those without nodal metastases, R1 status was the strongest predictor of poor outcome (Farges et al. 2011).

Future Liver Remnant

The future liver remnant volume required to avoid postoperative liver failure is similar in intrahepatic cholangiocarcinoma to other liver tumors (25% with normal liver function) (Mazzaferro et al. 2020). However, iCCA commonly arises in patients with chronic liver disease, where a cut-off of 40% is generally acceptable (Mazzaferro et al. 2020). To increase the safety of extended liver resection with inadequate future liver remnant, limited data suggests portal vein embolization may be used albeit with a less predictable response in chronic liver disease (Glantzounis et al. 2017). The ALPPS procedure has been used for locally advanced iCCA with encouraging rates of R0 resection and long-term survival (Bednarsch et al. 2019; J. Li et al. 2020a) but with higher morbidity and mortality thereby limiting its use (Serenari et al. 2016).

Lymphadenectomy

Lymph node metastases occur in up to 30–40% of iCCA when lymphadenectomy is performed (de Jong et al. 2011). Although lymph node positivity is an important prognostic factor after liver resection (Clark et al. 2011), therapeutic porta hepatitis lymphadenectomy does not improve overall survival (Shimada et al. 2009). The NCCN guidelines recommend lymphadenectomy with a minimum yield of six nodes for iCCA (NCCN 2021). This is likely to become more important with nodal staging being important role in stratification for adjuvant therapy (Mazzaferro et al. 2020).

Minimally Invasive Surgery

A minimally invasive approach to liver resection for iCCA may be possible with equivalent overall survival and lymph node yield and results with improved short-term outcomes in selected cases (W. Lee et al. 2016; Ratti et al. 2016); overall in most situations however it is not appropriate. A robotic approach may address some of these limitations and a study of 34 iCCA resections (15 robotic, 19 open), equivalent oncological outcomes were achieved (Shapera et al. 2022).

Outcomes after Resection

Long-term outcomes after resection for iCCA remain poor. Meta-analysis has demonstrated a median survival of 28 months with 5-year overall survival of 30% (Table 4) (Mavros et al. 2014). Important prognostic factors include tumor size, the presence of multifocal disease, lymph node metastases, and vascular invasion (Mavros et al. 2014). Multifocal disease outcomes appear equivalent between surgery and transarterial chemoembolization or hepatic artery infusional therapy (Wright et al. 2018).

Re-resection

The liver is the commonest site of recurrence within two years of resection (83%) but recurrence occurring after two years is usually extrahepatic (61%) (Doussot et al. 2016). The prognosis is generally poor in the setting of recurrence, however, some patients with liver-only recurrence may be suitable for re-resection (Spolverato et al. 2016). In a multicenter study of 400 patients with recurrent iCCA, resection of recurrent liver-only disease improved median survival (26.7 months) compared to intra-arterial therapy (9.6 months) or standard chemotherapy (16.8 months) (Spolverato et al. 2016).

Liver Transplantation

Historically, liver transplantation has been contraindicated for iCCA due to poor outcomes and post-transplant survival (1-year survival < 50%) (Goldstein et al. 1993; Pichlmayr et al. 1995). However, recent studies have demonstrated better survival in patients found to have iCCA or combined hepatocellular-cholangiocarcinoma in the explant when originally transplanted for hepatocellular carcinoma (Facciuto et al. 2015; Sapisochin et al. 2016; Sotiropoulos et al. 2008; Vilchez et al. 2016). These results

Table 4 Selected outcomes after liver resection for intra-hepatic cholangiocarcinoma.

Article, country	Study period	Number of patients	Morbidity <90 days	Mortality <90 days	5-year survival
Spolverato et al. (2015) Multinational	1990–2013 Multi-center	584	-	-	22%
Li et al. (2011) China	2001–2008 Single-center	115	35%	2%	17%
Ali et al. (2013) USA	1997–2011 Single-center	121	43%	1%	Vascular resection 44% No vascular resection: 23%
Tabrizian et al. (2015) USA	1995–2011 Single-center	82	-	1%	40%
Bektas et al. (2015) Germany	1995–2010 Single-center	221	30%	5%	36% 3 year-survival
Luo et al. (2014) China	2007–2011 Single-center	1333	12%	1%	17%
Kim et al. (2015) Korea	1995–2012 Single-center	215	30%	1%	Lymph node dissection: 30% Non-lymph node dissection: 43%
Si et al. (2019) China	2006–2010 Single-center	702	26%	4.4%	Anatomical resection: 36% Non-anatomical resection: 25%

combined with success with hilar cholangiocarcinoma using the Mayo Clinic Protocol have reintroduced liver transplantation as a treatment for cholangiocarcinoma in two ways.

Liver transplant for iCCA may be considered in the following situations: (1) in patients with early disease and cirrhosis; a multi-center study of 48 patients with a single tumor ≤2cm had a 5-year survival of 65% (Sapisochin et al. 2016). This is being studied in a prospective multi-center trial (Mazzaferro et al. 2020). (2) Unresectable i-CCA due to local invasion and location, may be suitable for liver transplantation following neoadjuvant chemotherapy (Lunsford et al. 2018; McMillan et al. 2022). In a series of 18 patients over 12 years, liver transplantation was used to treat patients with locally advanced/unresectable iCCA that demonstrated stability for 6 months on neoadjuvant chemotherapy (McMillan et al. 2022). The authors reported a 1-, 3- and 5-year overall survival of 100%, 71% and 57% respectively (McMillan et al. 2022); validation with multicentre clinical trials is required.

Key Take Home Messages

1. Surgery is the only curative treatment for intrahepatic cholangiocarcinoma.
2. Liver resection should aim for an R0 resection and include a lymphadenectomy for nodal staging.
3. Portal vein embolization or ALPPS can be used to improve the safety of liver resection in patients with inadequate future liver remnant.
4. A minimally invasive approach may be appropriate in selected patients.
5. Liver transplantation remains experimental but can be considered as part of a clinical trial.
6. A treatment algorithm for perihilar cholangiocarinoma is outlined in Figure 8.

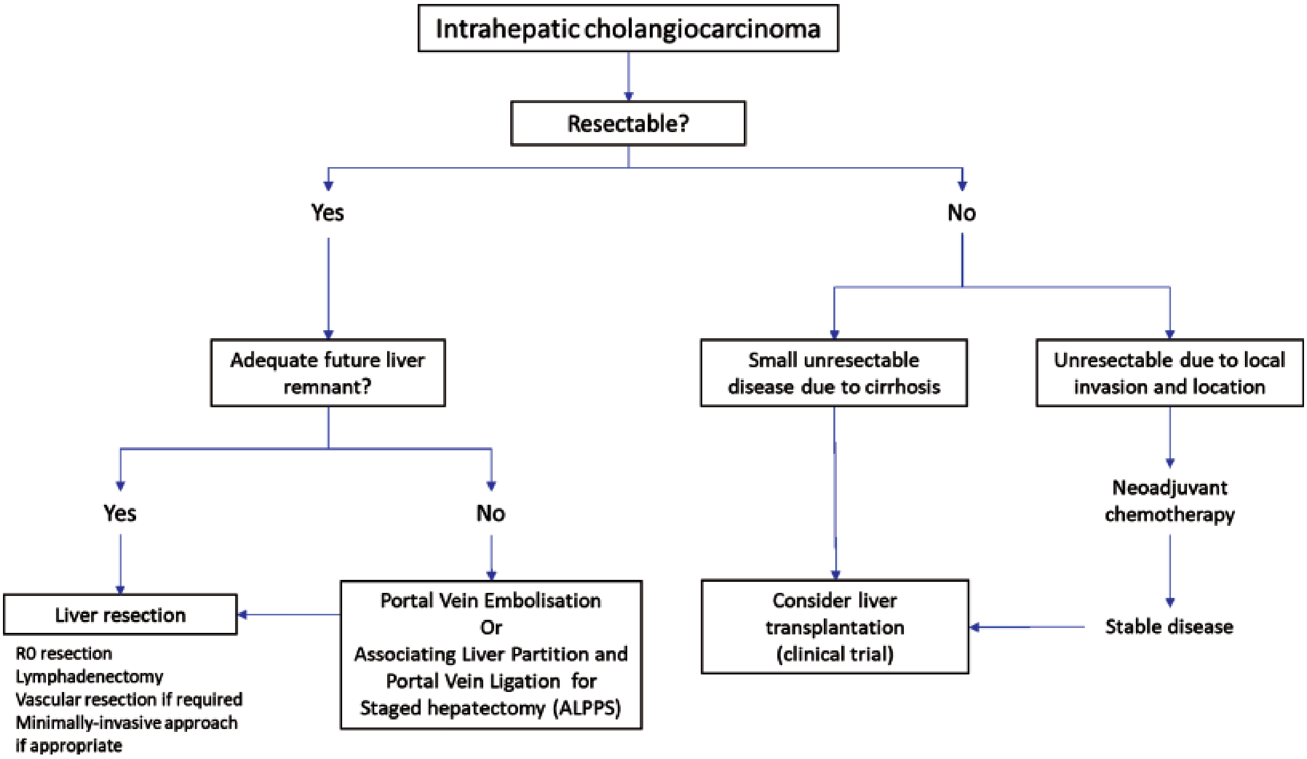
Intrahepatic cholangiocarcinoma
Resectable?
Yes
No
Adequate future liver remnant?
Yes
No
Liver resection
R0 resection
Lymphadenectomy
Vascular resection if required
Minimally-invasive approach if appropriate
Portal Vein Embolisation Or Associating Liver Partition and Portal Vein Ligation for Staged hepatectomy (ALPPS)
Small unresectable disease due to cirrhosis
Unresectable due to local invasion and location
Neoadjuvant chemotherapy
Stable disease
Consider liver transplantation (clinical trial)

Figure 8 Intrahepatic cholangiocarcinoma treatment algorithm.

Areas for Further Research

1. Optimized chemotherapy regimens
2. Improved targeted and Immunotherapy regimens
3. Predictive biomarkers

Trusted Websites for Further Reading

https://www.mayoclinic.org/diseases-conditions/cholangiocarcinoma/symptoms-causes/syc-20352408

https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-digestive-system-tumors/cholangiocarcinoma

References

Abbas, S. and Sandroussi, C. (2013). Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford)* 15 (7): 492–503. doi: 10.1111/j.1477-2574.2012.00616.x.

Acher, A.W., Weber, S.M., and Pawlik, T.M. (2021). Liver transplantation for perihilar cholangiocarcinoma: patient selection and outcomes. *Expert Rev Gastroenterol Hepatol* 15 (5): 555–566. doi: 10.1080/17474124.2021.1890584.

Al Mahjoub, A., Menahem, B., Fohlen, A. et al. (2017). Preoperative biliary drainage in patients with resectable perihilar cholangiocarcinoma: is percutaneous transhepatic biliary drainage safer and more effective than endoscopic biliary drainage? A meta-analysis. *J Vasc Interv Radiol* 28 (4): 576–582. doi: 10.1016/j.jvir.2016.12.1218.

Ali, S.M., Clark, C.J., Zaydfudim, V.M. et al. (2013). Role of major vascular resection in patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 20 (6): 2023–2028. doi: 10.1245/s10434-012-2808-2.

Alikhanov, R., Dudareva, A., Trigo, M.A., and Serrablo, A. (2021). Vascular resection for intrahepatic cholangiocarcinoma: current considerations. *J Clin Med* 10 (17). doi: 10.3390/jcm10173829.

Aloia, T.A., Charnsangavej, C., Faria, S. et al. (2007). High-resolution computed tomography accurately predicts resectability in hilar cholangiocarcinoma. *Am J Surg* 193 (6): 702–706. doi: 10.1016/j.amjsurg.2006.10.024.

Amin, M.B., Edge, S.B., Greene, F.L. (eds.) (2017). *AJCC Cancer Staging Manual*, (Vol. 1024). New York: Springer.

Aoba, T., Ebata, T., Yokoyama, Y. et al. (2013). Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. *Ann Surg* 257 (4): 718–725. doi: 10.1097/SLA.0b013e3182822277.

Bednarsch, J., Czigany, Z., Lurje, I. et al. (2019). The role of ALPPS in intrahepatic cholangiocarcinoma. *Langenbecks Arch Surg* 404 (7): 885–894. doi: 10.1007/s00423-019-01838-2.

Bektas, H., Yeyrek, C., Kleine, M. et al. (2015). Surgical treatment for intrahepatic cholangiocarcinoma in Europe: a single center experience. *J Hepatobiliary Pancreat Sci* 22 (2): 131–137. doi: 10.1002/jhbp.158.

Blechacz, B., Komuta, M., and Roskams, T. et al. (2011). Clinical diagnosis and staging of cholangiocarcinoma, *Nat Rev Gastroenterol Hepatol*, 8 (9): 512-522. doi: 10.1038/nrgastro.2011.131.

Bridgewater, J., Galle, P.R., Khan, S.A. et al. (2014). Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 60 (6): 1268–1289. doi: 10.1016/j.jhep.2014.01.021.

Cillo, U., Fondevila, C., Donadon, M. et al. (2019). Surgery for cholangiocarcinoma. *Liver Int* 39 (Suppl 1): 143–155. doi: 10.1111/liv.14089.

Clark, C.J., Wood-Wentz, C.M., Reid-Lombardo, K.M. et al. (2011). Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. *HPB (Oxford)* 13 (9): 612–620. doi: 10.1111/j.1477-2574.2011.00340.x.

Conci, S., Vigano, L., Ercolani, G. et al. (2020). Outcomes of vascular resection associated with curative intent hepatectomy for intrahepatic cholangiocarcinoma. *Eur J Surg Oncol* 46 (9): 1727–1733. doi: 10.1016/j.ejso.2020.04.007.

Corvera, C.U., Blumgart, L.H., Akhurst, T. et al. (2008). 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. *J Am Coll Surg* 206 (1): 57–65. doi: 10.1016/j.jamcollsurg.2007.07.002.

Darwish Murad, S., Kim, W.R., Harnois, D.M. et al. (2012). Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 143 (1): 88–98 e83; quiz e14. doi: 10.1053/j.gastro.2012.04.008.

de Jong, M.C., Marques, H., Clary, B.M. et al. (2012). The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. *Cancer* 118 (19): 4737–4747. doi: 10.1002/cncr.27492.

de Jong, M.C., Nathan, H., Sotiropoulos, G.C. et al. (2011). Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 29 (23): 3140–3145. doi: 10.1200/JCO.2011.35.6519.

DeOliveira, M.L., Cunningham, S.C., Cameron, J.L. et al. (2007). Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 245 (5): 755–762. doi: 10.1097/01.sla.0000251366.62632.d3.

Doussot, A., Gonen, M., Wiggers, J.K. et al. (2016). Recurrence patterns and disease-free survival after resection of intrahepatic cholangiocarcinoma: preoperative and postoperative prognostic models. *J Am Coll Surg* 223 (3): 493–505 e492. doi: 10.1016/j.jamcollsurg.2016.05.019.

Ebata, T., Yokoyama, Y., Igami, T. et al. (2012). Portal vein embolization before extended hepatectomy for biliary cancer: current technique and review of 494 consecutive embolizations. *Dig Surg* 29 (1): 23–29. doi: 10.1159/000335718.

Endo, I., Gonen, M., Yopp, A.C. et al. (2008). Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 248 (1): 84–96. doi: 10.1097/SLA.0b013e318176c4d3.

Ethun, C.G., Lopez-Aguiar, A.G., Anderson, D.J. et al. (2018). Transplantation versus resection for hilar cholangiocarcinoma: an argument for shifting treatment paradigms for resectable disease. *Ann Surg* 267 (5): 797–805. doi: 10.1097/SLA.0000000000002574.

Facciuto, M.E., Singh, M.K., Lubezky, N. et al. (2015). Tumors with intrahepatic bile duct differentiation in cirrhosis: implications on outcomes after liver transplantation. *Transplantation* 99 (1): 151–157. doi: 10.1097/TP.0000000000000286.

Farges, O., Fuks, D., Boleslawski, E. et al. (2011). Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg* 254 (5): 824–829; discussion 830. doi: 10.1097/SLA.0b013e318236c21d.

Farges, O., Regimbeau, J.M., Fuks, D. et al. (2013). Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 100 (2): 274–283. doi: 10.1002/bjs.8950.

Ferrero, A., Lo Tesoriere, R., Vigano, L. et al. (2009). Preoperative biliary drainage increases infectious complications after hepatectomy for proximal bile duct tumor obstruction. *World J Surg* 33 (2): 318–325. doi: 10.1007/s00268-008-9830-3.

Franken, L.C., Olthof, P.B., Erdmann, J.I. et al. (2021). Short- and long-term outcomes after hemihepatectomy for perihilar cholangiocarcinoma: does left or right side matter? *Hepatobiliary Surg Nutr* 10 (2): 154–162. doi: 10.21037/hbsn-19-948.

Furusawa, N., Kobayashi, A., Yokoyama, T. et al. (2014). Surgical treatment of 144 cases of hilar cholangiocarcinoma without liver-related mortality. *World J Surg* 38 (5): 1164–1176. doi: 10.1007/s00268-013-2394-x.

Glantzounis, G.K., Tokidis, E., Basourakos, S.P. et al. (2017). The role of portal vein embolization in the surgical management of primary hepatobiliary cancers. A systematic review. *Eur J Surg Oncol* 43 (1): 32–41. doi: 10.1016/j.ejso.2016.05.026.

Goldstein, R.M., Stone, M., Tillery, G.W. et al. (1993). Is liver transplantation indicated for cholangiocarcinoma? *Am J Surg* 166 (6): 768–771; discussion 771-762. doi: 10.1016/s0002-9610(05)80696-8.

Hameed, A., Pang, T., Chiou, J. et al. (2016). Percutaneous vs. endoscopic pre-operative biliary drainage in hilar cholangiocarcinoma - a systematic review and meta-analysis. *HPB (Oxford)* 18 (5): 400–410. doi: 10.1016/j.hpb.2016.03.002.

Heimbach, J.K., Gores, G.J., Haddock, M.G. et al. (2004). Liver transplantation for unresectable perihilar cholangiocarcinoma. *Semin Liver Dis* 24 (2): 201–207. doi: 10.1055/s-2004-828896.

Hewitt, D.B., Brown, Z.J., and Pawlik, T.M. (2022). Surgical management of intrahepatic cholangiocarcinoma. *Expert Rev Anticancer Ther* 22 (1): 27–38. doi: 10.1080/14737140.2022.1999809.

Hochwald, S.N., Burke, E.C., Jarnagin, W.R. et al. (1999). Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. *Arch Surg* 134 (3): 261–266. doi: 10.1001/archsurg.134.3.261.

Hu, H.J., Wu, Z.R., Jin, Y.W. et al. (2019). Minimally invasive surgery for hilar cholangiocarcinoma: state of art and future perspectives. *ANZ J Surg* 89 (5): 476–480. doi: 10.1111/ans.14765.

Iacono, C., Ruzzenente, A., Campagnaro, T. et al. (2013). Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg* 257 (2): 191–204.

Jarnagin, W.R., Fong, Y., DeMatteo, R.P. et al. (2001). Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 234 (4): 507–517; discussion 517-509. doi: 10.1097/00000658-200110000-00010.

Kato, T., Tsukamoto, E., Kuge, Y. et al. (2002). Clinical role of (18) F-FDGPET for initial staging of patients with extrahepatic bile duct cancer. *Eur J Nucl Med Mol Imaging* 29 (8): 1047–1054. doi: 10.1007/s00259-002-0852-z.

Kennedy, T.J., Yopp, A., Qin, Y. et al. (2009). Role of preoperative biliary drainage of liver remnant prior to extended liver resection for hilar cholangiocarcinoma. *HPB (Oxford)* 11 (5): 445–451. doi: 10.1111/j.1477-2574.2009.00090.x.

Kim, D.H., Choi, D.W., Choi, S.H. et al. (2015). Is there a role for systematic hepatic pedicle lymphadenectomy in intrahepatic cholangiocarcinoma? A review of 17 years of experience in a tertiary institution. *Surgery* 157 (4): 666–675. doi: 10.1016/j.surg.2014.11.006.

Kimmings, A.N., van Deventer, S.J., Obertop, H. et al. (1995). Inflammatory and immunologic effects of obstructive jaundice: pathogenesis and treatment. *J Am Coll Surg* 181 (6): 567–581.

Kluge, R., Schmidt, F., Caca, K. et al. (2001). Positron emission tomography with [(18)F]fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. *Hepatology* 33 (5): 1029–1035. doi: 10.1053/jhep.2001.23912.

Krähenbühl, L., Schäfer, M., and Krähenbühl, S. (1998). Reversibility of hepatic mitochondrial damage in rats with long-term cholestasis. *J Hepatol* 28 (6): 1000–1007.

Lauterio, A., De Carlis, R., Centonze, L. et al. (2021). Current surgical management of peri-hilar and intra-hepatic cholangiocarcinoma. *Cancers (Basel)* 13 (15).

Lee, H.Y., Kim, S.H., Lee, J.M. et al. (2006). Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: combined CT and cholangiography with revised criteria. *Radiology* 239 (1): 113–121. doi: 10.1148/radiol.2383050419.

Lee, W., Park, J.H., Kim, J.Y. et al. (2016). Comparison of perioperative and oncologic outcomes between open and laparoscopic liver resection for intrahepatic cholangiocarcinoma. *Surg Endosc* 30 (11): 4835–4840. doi: 10.1007/s00464-016-4817-x.

Li, J., Moustafa, M., Linecker, M. et al. (2020a). ALPPS for locally advanced intrahepatic cholangiocarcinoma: did aggressive surgery lead to the oncological benefit? An international multi-center study. *Ann Surg Oncol* 27 (5): 1372–1384. doi: 10.1245/s10434-019-08192-z.

Li, J., Tan, X., Zhang, X. et al. (2020b). Robotic radical surgery for hilar cholangiocarcinoma: a single-centre case series. *Int J Med Robot* 16 (2): e2076. doi: 10.1002/rcs.2076.

Li, Y.M., Bie, Z.X., Guo, R.Q. et al. (2022). Effect of hepatic artery resection and reconstruction on the prognosis of patients with advanced hilar cholangiocarcinoma. *World J Gastrointest Oncol* 14 (4): 887–896. doi: 10.4251/wjgo.v14.i4.887.

Li, Y.Y., Li, H., Lv, P. et al. (2011). Prognostic value of cirrhosis for intrahepatic cholangiocarcinoma after surgical treatment. *J Gastrointest Surg* 15 (4): 608–613. doi: 10.1007/s11605-011-1419-8.

Liang, L., Li, C., Wang, M.-D. et al. (2021). The value of lymphadenectomy in surgical resection of perihilar cholangiocarcinoma: a systematic review and meta-analysis. *Int J Clin Oncol* 26 (9): 1575–1586. doi: 10.1007/s10147-021-01967-z.

Lim, J.H., Choi, G.H., Choi, S.H. et al. (2013). Liver resection for Bismuth type I and Type II hilar cholangiocarcinoma. *World J Surg* 37 (4): 829–837. doi: 10.1007/s00268-013-1909-9.

Lopera, J.E., Soto, J.A., and Munera, F. (2001). Malignant hilar and perihilar biliary obstruction: use of MR cholangiography to define the extent of biliary ductal involvement and plan percutaneous interventions. *Radiology* 220 (1): 90–96. doi: 10.1148/radiology.220.1.r01jl3990.

Lunsford, K.E., Javle, M., Heyne, K. et al. (2018). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 3 (5): 337–348.

Luo, X., Yuan, L., Wang, Y. et al. (2014). Survival outcomes and prognostic factors of surgical therapy for all potentially resectable intrahepatic cholangiocarcinoma: a large single-center cohort study. *J Gastrointest Surg* 18 (3): 562–572. doi: 10.1007/s11605-013-2447-3.

Mantel, H.T., Westerkamp, A.C., Sieders, E. et al. (2016). Intraoperative frozen section analysis of the proximal bile ducts in hilar cholangiocarcinoma is of limited value. *Cancer Med* 5 (7): 1373–1380. doi: 10.1002/cam4.693.

Masselli, G., Manfredi, R., Vecchioli, A., and Gualdi, G. (2008). MR imaging and MR cholangiopancreatography in the preoperative evaluation of hilar cholangiocarcinoma: correlation with surgical and pathologic findings. *Eur Radiol* 18 (10): 2213–2221. doi: 10.1007/s00330-008-1004-z.

Mavros, M.N., Economopoulos, K.P., Alexiou, V.G., and Pawlik, T.M. (2014). Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: systematic Review and Meta-analysis. *JAMA Surg* 149 (6): 565–574. doi: 10.1001/jamasurg.2013.5137.

Mazzaferro, V., Gorgen, A., Roayaie, S. et al. (2020). Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol* 72 (2): 364–377. doi: 10.1016/j.jhep.2019.11.020.

McMillan, R.R., Javle, M., Kodali, S. et al. (2022). Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. *Am J Transplant* 22 (3): 823–832. doi: 10.1111/ajt.16906.

Murakami, Y., Uemura, K., Sudo, T. et al. (2011). Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. *Ann Surg Oncol* 18 (3): 651–658. doi: 10.1245/s10434-010-1325-4.

Nagino, M., Ebata, T., and Mizuno, T. (2021). Oncological superiority of right-sided hepatectomy over left-sided hepatectomy as surgery for perihilar cholangiocarcinoma: truth or biased view? *Ann Surg* 274 (1): 31–32. doi: 10.1097/sla.0000000000004534.

Nagino, M., Ebata, T., Yokoyama, Y. et al. (2013). Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann Surg* 258 (1): 129–140. doi: 10.1097/SLA.0b013e3182708b57.

NCCN. (2021). NCCN guidelines version 4.2021 hepatobiliary cancers. In: National Cancer Care Network.

Neuhaus, P., Jonas, S., Bechstein, W.O. et al. (1999). Extended resections for hilar cholangiocarcinoma. *Ann Surg* 230 (6): 808–818; discussion 819. doi: 10.1097/00000658-199912000-00010.

Neuhaus, P., Thelen, A., Jonas, S. et al. (2012). Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. *Ann Surg Oncol* 19 (5): 1602–1608. doi: 10.1245/s10434-011-2077-5.

Nimura, Y., Hayakawa, N., Kamiya, J. et al. (1990). Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. *World J Surg* 14 (4): 535–543; discussion 544. doi: 10.1007/bf01658686.

Olthof, P.B., Coelen, R.J.S., Wiggers, J.K. et al. (2017). High mortality after ALPPS for perihilar cholangiocarcinoma: case-control analysis including the first series from the international ALPPS registry. *HPB (Oxford)* 19 (5): 381–387. doi: 10.1016/j.hpb.2016.10.008.

Pichlmayr, R., Weimann, A., Oldhafer, K.J. et al. (1995). Role of liver transplantation in the treatment of unresectable liver cancer. *World J Surg* 19 (6): 807–813. doi: 10.1007/bf00299775.

Ratti, F., Cipriani, F., Ariotti, R. et al. (2016). Safety and feasibility of laparoscopic liver resection with associated lymphadenectomy for intrahepatic cholangiocarcinoma: a propensity score-based case-matched analysis from a single institution. *Surg Endosc* 30 (5): 1999–2010. doi: 10.1007/s00464-015-4430-4.

Ratti, F., Fiorentini, G., Cipriani, F. et al. (2020a). Perihilar cholangiocarcinoma: are we ready to step towards minimally invasiveness? *Updates Surg* 72 (2): 423–433. doi: 10.1007/s13304-020-00752-3.

Ratti, F., Fiorentini, G., Cipriani, F. et al. (2020b). Technical insights on laparoscopic left and right hepatectomy for perihilar cholangiocarcinoma. *Ann Surg Oncol* 27 (13): 5191–5192. doi: 10.1245/s10434-020-08647-8.

Ribero, D., Pinna, A.D., Guglielmi, A. et al., … Italian Intrahepatic Cholangiocarcinoma Study, G. (2012). Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. Arch Surg, 147(12), 1107–1113. doi: 10.1001/archsurg.2012.1962.

Ribero, D., Zimmitti, G., Aloia, T.A. et al. (2016). Preoperative cholangitis and future liver remnant volume determine the risk of liver failure in patients undergoing resection for hilar cholangiocarcinoma. *J Am Coll Surg* 223 (1): 87–97. doi: 10.1016/j.jamcollsurg.2016.01.060.

Rimola, J., Forner, A., Reig, M. et al. (2009). Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. *Hepatology* 50 (3): 791–798. doi: 10.1002/hep.23071.

Rosen, C.B., Heimbach, J.K., and Gores, G.J. (2010). Liver transplantation for cholangiocarcinoma. *Transpl Int* 23 (7): 692–697. doi: 10.1111/j.1432-2277.2010.01108.x.

Sakamoto, E., Nimura, Y., Hayakawa, N. et al. (1998). The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. *Ann Surg* 227 (3): 405–411. doi: 10.1097/00000658-199803000-00013.

Sapisochin, G., Facciuto, M., Rubbia-Brandt, L. et al., i, C. C. A. I. C.. (2016). Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. *Hepatology* 64 (4): 1178–1188. doi: 10.1002/hep.28744.

Schnitzbauer, A.A., Lang, S.A., Goessmann, H. et al. (2012). Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 255 (3): 405–414. doi: 10.1097/SLA.0b013e31824856f5.

Serenari, M., Zanello, M., Schadde, E. et al. (2016). Importance of primary indication and liver function between stages: results of a multicenter Italian audit of ALPPS 2012-2014. *HPB (Oxford)* 18 (5): 419–427. doi: 10.1016/j.hpb.2016.02.003.

Shapera, E.A., Ross, S., Syblis, C. et al. (2022). Analysis of oncological outcomes after robotic liver resection for intrahepatic cholangiocarcinoma. *Am Surg* 31348221093933. doi: 10.1177/00031348221093933.

Shimada, K., Sano, T., Nara, S. et al. (2009). Therapeutic value of lymph node dissection during hepatectomy in patients with intrahepatic cholangiocellular carcinoma with negative lymph node involvement. *Surgery* 145 (4): 411–416. doi: 10.1016/j.surg.2008.11.010.

Si, A., Li, J., Yang, Z. et al. (2019). Impact of anatomical versus non-anatomical liver resection on short- and long-term outcomes for patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 26 (6): 1841–1850. doi: 10.1245/s10434-019-07260-8.

Sotiropoulos, G.C., Kaiser, G.M., Lang, H. et al. (2008). Liver transplantation as a primary indication for intrahepatic cholangiocarcinoma: a single-center experience. *Transplant Proc* 40 (9): 3194–3195. doi: 10.1016/j.transproceed.2008.08.053.

Spolverato, G., Kim, Y., Alexandrescu, S. et al. (2016). Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. *Ann Surg Oncol* 23 (1): 235–243. doi: 10.1245/s10434-015-4642-9.

Spolverato, G., Vitale, A., Cucchetti, A. et al. (2015). Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer* 121 (22): 3998–4006. doi: 10.1002/cncr.29619.

Su, C.H., Tsay, S.H., Wu, C.C. et al. (1996). Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. *Ann Surg* 223 (4): 384–394.

Tabrizian, P., Jibara, G., Hechtman, J.F. et al. (2015). Outcomes following resection of intrahepatic cholangiocarcinoma. *HPB (Oxford)* 17 (4): 344–351. doi: 10.1111/hpb.12359.

Tan, E.K., Rosen, C.B., Heimbach, J.K. et al. (2020). Living donor liver transplantation for perihilar cholangiocarcinoma: outcomes and complications. *J Am Coll Surg* 231 (1): 98–110. doi: 10.1016/j.jamcollsurg.2019.12.037.

Tang, Z., Yang, Y., Zhao, Z. et al. (2018). The clinicopathological factors associated with prognosis of patients with resectable perihilar cholangiocarcinoma: a systematic review and meta-analysis. *Medicine (Baltimore)* 97 (34): e11999. doi: 10.1097/MD.0000000000011999.

Tillich, M., Mischinger, H.J., Preisegger, K.H. et al. (1998). Multiphasic helical CT in diagnosis and staging of hilar cholangiocarcinoma. *AJR Am J Roentgenol* 171 (3): 651–658. doi: 10.2214/ajr.171.3.9725291.

Tran, T.B., Ethun, C.G., Pawlik, T.M. et al. (2019). Actual 5-year survivors after surgical resection of hilar cholangiocarcinoma. *Ann Surg Oncol* 26 (2): 611–618. doi: 10.1245/s10434-018-7075-4.

Van Beers, B.E. (2008). Diagnosis of cholangiocarcinoma. *HPB (Oxford)* 10 (2): 87–93. doi: 10.1080/13651820801992716.

van der Gaag, N.A., Rauws, E.A., van Eijck, C.H. et al. (2010). Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 362 (2): 129–137. doi: 10.1056/NEJMoa0903230.

Vilchez, V., Shah, M.B., Daily, M.F. et al. (2016). Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database. *HPB (Oxford)* 18 (1): 29–34. doi: 10.1016/j.hpb.2015.10.001.

Vilgrain, V. (2008). Staging cholangiocarcinoma by imaging studies. *HPB (Oxford)* 10 (2): 106–109. doi: 10.1080/13651820801992617.

Vogl, T.J., Schwarz, W.O., Heller, M. et al. (2006). Staging of Klatskin tumours (hilar cholangiocarcinomas): comparison of MR cholangiography, MR imaging, and endoscopic retrograde cholangiography. *Eur Radiol* 16 (10): 2317–2325. doi: 10.1007/s00330-005-0139-4.

Wang, L., Lin, N., Xin, F. et al. (2019). A systematic review of the comparison of the incidence of seeding metastasis between endoscopic biliary drainage and percutaneous transhepatic biliary drainage for resectable malignant biliary obstruction. *World J Surg Oncol* 17 (1): 116. doi: 10.1186/s12957-019-1656-y.

Wright, G.P., Perkins, S., Jones, H. et al. (2018). Surgical resection does not improve survival in multifocal intrahepatic cholangiocarcinoma: a comparison of surgical resection with intra-arterial therapies. *Ann Surg Oncol* 25 (1): 83–90. doi: 10.1245/s10434-017-6110-1.

Xiang, S., Lau, W.Y., and Chen, X.P. (2015). Hilar cholangiocarcinoma: controversies on the extent of surgical resection aiming at cure. *Int J Colorectal Dis* 30 (2): 159–171. doi: 10.1007/s00384-014-2063-z.

Yu, W., Gu, Z., Shi, S. et al. (2014). Effect evaluation of vascular resection for patients with hilar cholangiocarcinoma: original data and meta-analysis. *Cell Biochem Biophys* 69 (3): 509–516. doi: 10.1007/s12013-014-9825-7.

Zaborowski, A., Heneghan, H.M., Fiore, B. et al. (2020). Neoadjuvant chemoradiotherapy and liver transplantation for unresectable hilar cholangiocarcinoma: the Irish experience of the mayo protocol. *Transplantation* 104 (10): 2097–2104. doi: 10.1097/TP.0000000000003114.

Chemotherapy

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Adjuvant Therapy

Outcomes remain poor for operable cholangiocarcinoma even with complete curative intent resections. Current evidence supports a role for adjuvant fluoropyrimidine based chemotherapy in appropriately selected patients, with some caveats. Prospective phase III chemotherapy trials have been largely negative, with only two suggesting a benefit with oral fluoropyrimidines. The role of adjuvant (chemo) radiotherapy is also debated (see radiation section of chapter). Guidelines vary by institution but nevertheless, it is generally agreed that patients with R1 resections or lymph node involvement should be considered for adjuvant therapy (Shroff et al. 2019; Valle et al. 2016).

The only phase III trial to report a statistically significant survival benefit is the JCOG 1202/ASCOT trial which randomized 440 patients with R0 or R1 resection of biliary tract cancers to observation, or 6 months of the fluoropyrimidine S-1. 3-year overall survival (OS) was longer in the adjuvant S-1 group at 77.1% (95% CI 70.9–82.1%) compared to surgery alone 67.6% (95% CI 61.0–73.3%; Hazard Ratio (HR) 0.694 95% CI 0.514–0.935). Three-year relapse free survival (RFS) was also improved in the S-1 group 62.4% (95% CI 55.6–68.4%) compared to 50.9% (95% CI 44.1–57.2%; HR 0.797, 95% CI 0.613–1.035). The most common grade 3–4 adverse event was cholangitis in 7.2% (Ikeda et al. 2022). This study was performed on an Asian population, and results have not been reproducible in other populations.

Capecitabine is another oral fluoropyrimidine with potential adjuvant activity. The phase III BILCAP trial recruited 447 patients with macroscopically complete resection of cholangiocarcinoma randomized to 6 months of oral capecitabine 1250 mg/m2, or observation. BILCAP failed to reach its primary endpoint of improved OS in the ITT population, but did demonstrated a benefit for capecitabine in a per protocol analysis (adjusted HR 0.75, 95% CI 0.58–0.97). 32% of patients discontinued capecitabine due to toxicity, most commonly hand-foot syndrome. There was also one case of grade four coronary event (Primrose et al. 2019).

To date no phase III trial has demonstrated a benefit to adjuvant intravenous chemotherapy compared to observation. For example, the PRODIGE-12 trial randomized 194 patients with R0/R1 resection of localized cholangiocarcinoma to 12 cycles of gemcitabine and oxaliplatin, or observation. There was a statistically insignificant difference in median RFS (30.4 months vs 18.5 months) and OS (75.8 vs 50.8 months) in favor of chemotherapy No subgroup with clear benefit was identified (Edeline et al. 2019). Similarly, ESPAC-3 evaluated the role of adjuvant single agent gemcitabine or 5-fluoruracil/folinic acid in resected (R0 or R1) periampullary adenocarcinoma including 96 (22%) patients with localized intrapancreatic cholangiocarcinoma. There was no improvement in OS with chemotherapy for the whole population in unadjusted analyses. The median OS for the biliary subgroup was 27.2 months (95% CI, 15.4–31.9), 18.3 months (95% CI, 12.9–28.7), and 19.5 months (95% CI, 16.2–36.1) for the observation, 5-fluorouracil, and gemcitabine groups respectively (Neoptolemos et al. 2012). It should be noted that this trial was not powered to detect a difference in survival for the cholangiocarcinoma subgroup.

Two trials examining newer systemic treatments are ongoing. The phase III ACTICCA-01 trial initially compared adjuvant gemcitabine and cisplatin, to observation for resected cholangiocarcinoma and gallbladder carcinomas. Following the BILCAP results, the control arm was amended to capecitabine and a sub-study was included to address the question of adjuvant chemoradiotherapy (see radiation section). The phase II ACCORD trial evaluates adjuvant immunotherapy (camrelizumab (anti PD-1)) combined with capecitabine chemoradiation, compared with observation for patients with high-risk resectable extrahepatic cholangiocarcinoma and gallbladder cancer. High-risk is defined as R1 resection or R0 resection with T2-4 or N1 pathology.

There is some data to support adjuvant systemic therapy for resected cholangiocarcinoma, but room for improvement; new approaches and trials are warranted. Given the poor outcomes with resection alone it is recommended that risks and benefits of adjuvant chemotherapy should be discussed for all suitable patients.

Adjuvant Chemoradiotherapy

See radiotherapy section.

Neoadjuvant Treatment

Neoadjuvant therapy is not standard practice in the treatment of cholangiocarcinoma. There is a lack of strong prospective trial data, and most evidence is from retrospective series. Most neoadjuvant studies for unresectable extrahepatic cholangiocarcinoma used combined chemoradiotherapy with reports of pathological response and successful R0 resection. This will be discussed in more detail in the radiotherapy section of this chapter.

A meta-analysis identified two single center studies in which patients with intrahepatic cholangiocarcinoma received neoadjuvant chemotherapy (Rizzo and Brandi 2021). In one prospective study, 8 of 22 patients with unresectable cholangiocarcinoma or gallbladder carcinoma received neoadjuvant gemcitabine. 4 achieved R0 and 4 R1 resection with a group median survival of 19.3 months compared to 7.5 months for those treated with chemotherapy alone ($p = 0.032$) (Kato et al. 2013). In a retrospective study of 74 patients with unresectable intrahepatic cholangiocarcinoma, 39 patients received neoadjuvant chemotherapy (mostly gemcitabine doublet). Median survival was comparable to patients with upfront resectable disease without chemotherapy:24.1 months compared to 25.7 months (HR 1.23, 95% CI 0.77 to 1.97). In contrast, patients with unresectable disease treated with chemotherapy alone had a shorter median survival of 7.8 months (HR 3.80, 95% CI 2.29 to 6.30) (Le Roy et al. 2017).

Prospective trials looking at neoadjuvant systemic therapy are in progress, including the phase II DEBATE trial assessing the effect of neoadjuvant cisplatin and gemcitabine with or without durvalumab (ClinicalTrials.gov 2020) and a phase II trial of triplet chemotherapy with gemcitabine cisplatin and nab-paclitaxel (ClinicalTrials.gov 2022).

First Line Treatment of Unresectable or Metastatic Disease

Chemotherapy remains the standard of care for unresectable or metastatic cholangiocarcinoma despite relatively poor outcomes. The standard regimen is gemcitabine-based doublet, often with cisplatin or oxaliplatin. Gemcitabine combined with nab-paclitaxel or capecitabine has also shown some activity. These combinations have not been directly compared in a trial setting.

Chemotherapy

The strongest evidence for first line gemcitabine and cisplatin comes from the randomized phase III ABC-02 trial which compared gemcitabine + cisplatin, to gemcitabine. Median OS was 3.6 months greater with the doublet (HR 0.64 95%CI 0.52–0.80, $p < 0.001$). Tumor control rate was greater in the combination arm at 81.4% compared to 71.8% for gemcitabine ($P = 0.049$). HR for death was in favor of combination for both intrahepatic and extrahepatic CCA subgroups. Grade 3–4 neutropenia was more common in patients receiving combination (25.3% vs 16.6%) but there were no increased infections.

The phase II GERCOR trial of GEMOX in advanced biliary tract cancer included 33 untreated patients including 16 with intrahepatic and 4 with extrahepatic cholangiocarcinoma. Overall response rate (ORR) was 36% and median OS for the first-line cohort was 15.4 months. Most common grade 3–4 toxicities were myelosuppression, and peripheral sensory neuropathy (André et al. 2004).

A phase II trial of gemcitabine and nab-paclitaxel in 74 patients with advanced or metastatic cholangiocarcinoma demonstrated an ORR of 30%, median PFS of 7.7 months, and median OS of 12.4 months (95% CI 9.2–15.9). The 6-month PFS of 61% observed in this trial however did not meet the pre-specified threshold of 70% (Sahai et al. 2018). Moreover, 82% experienced a grade 3 or higher adverse events.

Fluoropyrimidine based regimens such as capecitabine with oxaliplatin (CAPOX) or infusional 5-FU with oxaliplatin (FOLFOX) should be considered for patients with biliary obstruction. A South Korean phase III randomized study comparing CAPOX to GEMOX demonstrated non-inferiority of CAPOX in an Asian population based on 6-month PFS with a pre-specified non-inferiority margin of 15%. Out of 222 randomized patients, 116 had a biliary primary. Median OS was similar for the ITT population; 10.4 months for CAPOX and 10.6 months for GEMOX, and 6-month PFS of 45% and 47% respectively. The HR for death in the cholangiocarcinoma subgroup was 1.034 (95% CI 0.691–1.584). There was no significant difference in the rates of grade 3–4 adverse events (Kim et al. 2019).

Triplet combinations are not widely used due to toxicity and lack of evidence. No OS nor PFS benefit was demonstrated for FOLFORINOX compared to gemcitabine and cisplatin in the phase II PRODIGE 38 AMEBICA trial (Phelip et al. 2022). Gemcitabine, cisplatin, and nab-paclitaxel combination has been explored in a single arm phase II study of 45 cholangiocarcinoma patients. The median OS was not reached for the intrahepatic group (95% CI 13.6-NE), and was 13.2 months (95% CI 1.8-NE) for the extrahepatic group. This combination is yet to be evaluated in a prospective phase III trial (Shroff et al. 2019).

Adding immunotherapy to chemotherapy may confer longer term disease control in patients with advanced cholangiocarcinoma. The phase III TOPAZ-1 trial randomized 685 patients with untreated unresectable, recurrent (> 6 months since adjuvant therapy) or metastatic biliary tract cancers to gemcitabine and cisplatin with either durvalumab or placebo. Preliminary results showed a small improvement in median OS (12.8 months vs 11.5 months; HR 0.8 95% CI 0.66–0.97), with benefits across all disease locations and PD-L1 expression. Rates of grade 3–4 adverse events were similar: 62.7% with durvalumab and 64.9% for placebo (Oh et al. 2020). However, the modest survival benefit needs to be weighed against the potential cost of treatment.

Single agent chemotherapy is an option for patients with poorer performance status, however response rates and survival outcomes are generally inferior to doublet regimens, as outlined in Table 5.

Non-Cytotoxic Systemic Therapy

A few trials have demonstrated activity of immunotherapy and targeted therapy in pretreated cholangiocarcinoma, but it is not yet known whether these drugs (excluding durvalumab) will be active in the first-line setting. The FIGHT-302 and PROOF-301 trials are comparing FGFR inhibitors pemigatinib and infigratinib against gemcitabine and cisplatin in the first line setting; results are pending (Bekaii-Saab et al. 2020; Makawita et al. 2020).

Table 5 Table of studies of including patients treated with first-line single agent chemotherapy in patients with metastatic cholangiocarcinoma.

Regimen	Study	Dose and schedule	N	Response rate (%)	Median OS (months)
Leucovorin Modulated Fluorouracil	Choi et al. 2000 (Choi et al. 2000)	FU 375 mg/m^2 + LV 25 mg/m^2 on days 1 to 5 every 3–4 weeks.	28*	32	6 (Range 1–16)
	Chen et al. 1998 (Chen et al. 1998)	2600MG/M2 5-FU + 150MG LV OVER 24 HOURS. WEEKLY FOR 6 WEEKS.	19*	33	7
Gemcitabine	Penz et al. 2001 (Penz et al. 2001)	2 weekly gemcitabine 2200 mg/m2	32*	22	11.5 (range 3.0–24.0)
	Okusaka et al. 2010 (Okusaka et al. 2010)	gemcitabine 1000 mg m−2 on days 1, 8 and 15 of a 28-day cycle	42*	11.9	^8.0 (95% CI 6.1–16.0)
	Novarino et al. 2013 (Novarino et al. 2013)	Gemcitabine 1250 mg/m2 days 1 and 8 of 21 day cycle	18*	0	8.3 months (95% CU 4.7–12.9)
	Valle et al. 2010 (Valle et al. 2010)	Gemcitabine 1000 mg/m2 on days 1, 8, 15 of 28 day cycle	206*	^11.6	8.1 months (95% CI, 7.1 to 8.7)
	Sasaki et al. 2013 (Sasaki et al. 2013)	Gemcitabine 100 mg/m2 on days 1, 8, 15 of 28 day cycle	18^	5.6	15.0
Capecitabine	Patt et al. 2004 (Patt et al. 2004)	Capecitabine 1000 mg/m2 BD days 1–14 of 21 day cycle.	18^	6	8.1 (95% CI 7.4–8.9)

* Includes gallbladder carcinoma
^ Excludes gallbladder carcinoma

Second Line Treatment and Beyond

Chemotherapy

Patients who progress on first-line treatment are generally limited to alternative chemotherapy regimens or trial referral provided they remain well. 5-Fluorouracil based regimens can be used for patients who have previously received gemcitabine-based regimens and vice versa, but the potential survival gains are small and may come at the expense of quality of life. FOLFOX6, and 5-FU with liposomal irinotecan have been evaluated in second line trials, however the data for many other regimens have been extrapolated from first-line studies.

The ABC-06 phase III open label trial randomized 162 patients with advanced biliary tract cancer and ECOG of 0 or 1 to modified FOLFOX6 and active symptom control, or active symptom control alone following radiological progression on cisplatin and gemcitabine combination. There was only a modest improvement in median OS for the chemotherapy arm: 6.2 months (95% CI 5.4–7.6) compared to 5.3 months (95% CI 44.1–5.8). However, there was improved OS for the FOLFOX6 group 50.6% (95% CI 39.3–60.9) at 6 months compared to 35.5% (95% CI 25.2–46) for active symptom control, and 25.9% at 12 months compared to 11.4% suggesting a subset of patients may survive longer with chemotherapy. However the rates of grade 3–5 adverse events was higher with FOLFOX (69% v 52%), and there were three chemotherapy-related deaths (Lamarca et al. 2021). FOLFOX6 therefore represents a standard of care option for second line therapy in suitable patients with preserved performance status.

The randomized phase 2b NIFTY trial compared liposomal irinotecan, fluorouracil, and leucovorin combination to fluorouracil and leucovorin in patients who had progressed on gemcitabine and cisplatin. This trial reported an improved PFS of 7.1 months for the intervention arm compared to 1.4 months (HR 0.56, 95% CI 0.39–0.81), and OS of 8.6 months compared to 5.5 months (HR 0.68 95% CI 0.48–0.98). However, this was likely skewed by the results of the gallbladder subgroup.HR for OS for the gallbladder group was 0.29 (95% CI 0.14–0.58) compared to 0.86 (95% CI 0.50–1.48) for intrahepatic, and 1.06 (95% CI 0.53–2.16) for the extrahepatic subgroup. Serious adverse events were reported in 42% of patients in the irinotecan arm compared to 24%, and fatal adverse events were identified in 6% compared to 1% for the control arm (Yoo et al. 2021).

Patients who have not had gemcitabine in the first-line setting may be treated with GEMOX which was shown in the phase II GERCOR trial to have activity in patients who had prior chemotherapy. A response rate of 22%, PFS of 3.9 months, and OS of 7.6 months was reported, however patients with gallbladder carcinoma represented 33% of this group (André et al. 2004).

Addition of bevacizumab to FOLFIRI or GEMOX has been evaluated in small cohorts but is not recommended due to paucity of data (Guion-Dusserre et al. 2015; Zhu et al. 2010). Similarly regorafenib was found to have no survival benefit compared to placebo (Demols et al. 2020).

Non-Cytotoxic Systemic Therapy

Molecular analyses of cholangiocarcinoma have shown that this is a diverse group of cancers rich in-molecular aberrations, many with prognostic and predictive implications. The frequencies of these mutations vary widely based on anatomical, pathological, and geographical distribution (Churi et al. 2014; Nakamura et al. 2015; Lowery et al. 2018; Zou et al. 2014; Javle et al. 2016) (see Figure 9). There is a growing body of evidence that the use of matching therapeutic agents can confer improved response rates and longer survival compared to standard cytotoxic therapy. In the MOSCATO-01 trial 34 of 43 patients with previously treated advanced biliary tract cancer underwent genetic sequencing, with 31 found to have at least one molecular aberration. 18 of these patients were able to undergo treatment with a corresponding drug with an objective response rate of 33% and disease control rate of 88%, and a median PFS of 5.2 months (95% CI, 1.7–15.9) (Verlingue et al. 2017). Microsatellite instability is uncommon in cholangiocarcinoma with a prevalence of 2–5% but is significant as it can predict for response to checkpoint inhibitor immunotherapy (Bonneville et al. 2017; Piha-Paul et al. 2020).

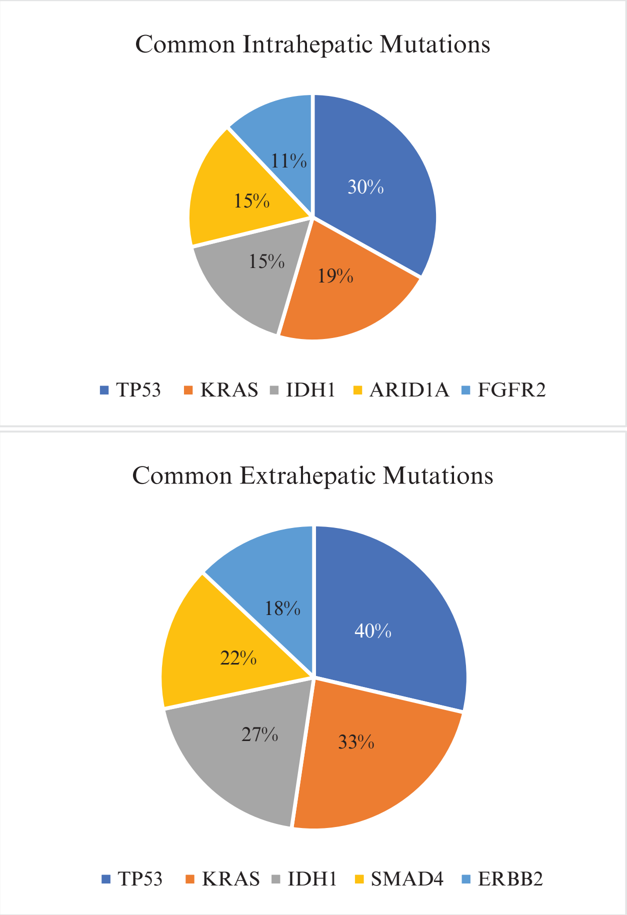

Figure 9 Pie chart of common mutations in intrahepatic and extrahepatic cholangiocarcinoma based on larger molecular profiling studies (Churi et al. 2014; Nakamura et al. 2015; Lowery et al. 2018; Zou et al. 2014). *N.B: some of these mutations are not mutually exclusive.*

Intrahepatic Cholangiocarcinoma

Tumors Harboring Targetable Mutations

IDH1 mutations are seen in up to 30% of intrahepatic cholangiocarcinoma (Lowery et al. 2018), and trial data suggests a small survival benefit with IDH inhibitors. The phase III double-blind placebo-controlled ClarIDHy tria randomized 185 patients with previously treated advanced IDH-1 mutant cholangiocarcinoma to ivosedinib or placebo. 57% of patients in the placebo group crossed over to ivosedinib. Median PFS was 2.7 months (95% CI 1.6–4.2) compared to 1.4 months (95% CI 1.4–1.6) for placebo (HR 0.37; 95% CI 0.25–0.54). Median OS in the ITT population was 10.8 months (95% CI 7.7–17.6) for the ivosidenib group versus 9.7 months (4.8–12.1) for placebo.

Fibroblast growth factor receptors (FGFR) regulate cell proliferation, survival, migration, and angiogenesis, and aberrations are associated with oncogenesis (Javle et al. 2016). FGFR fusions and rearrangements are present in 13–17% of intrahepatic cholangiocarcinoma butrare in extrahepatic cholangiocarcinoma. The selective FGFR1-3 inhibitor pemigatinib has been approved in the US based on the phase II single arm FIGHT-202 trial which demonstrated activity in patients with pre-treated FGFR2 mutant cholangiocarcinoma. 37% of 108 patients achieved a response and had a longer OS of 30.1 months (95% CI 21.5-NE) compared to 13.7 months (95% CI 9.6–16.1) for non-responders. There were no responses in patients with other or no FGFR aberrations. Hyperphosphatemia, alopecia, diarrhea, and fatigue were most the most common adverse events (Abou-Alfa et al. 2020; Abou-Alfa et al. 2021). Other potential targetable mutations include BRAF, HER2 amplification (Javle et al. 2015; Subbiah et al. 2020).

Immunotherapy

Patients with MSI-H cholangiocarcinoma may respond well to checkpoint inhibitor immunotherapy. 22 patients with previously treated cholangiocarcinoma were included in the KEYNOTE-158 trial and treated with pembrolizumab with an ORR of 40.9% and a median PFS of 4.2 months (Range 2.1-NR) and OS of 24.3 months (Range 6.5-NR). Grade 3–5 adverse events occurred in 14.6% overall (Piha-Paul et al. 2020; Marabelle et al. 2020).

Doublet anti-PD-1 and anti-CTLA4 therapy may overcome immunotherapy resistance in microsatellite stable intrahepatic carcinomas. In the biliary tract cancer subgroup analysis of the CA2090-538 trial, 5 of 16 patients with MSS intrahepatic cholangiocarcinoma experienced tumor response for a duration of 3–14.8 months. Grade 3 to 4 immune mediated adverse events occurred in 15% of the cohort. No patients with extrahepatic cholangiocarcinoma responded (Klein et al. 2020).

Extrahepatic Cholangiocarcinoma

There are fewer data for targeted therapies in extrahepatic cholangiocarcinoma. The potential targets KRAS and HER2 amplification are more common than in intrahepatic carcinoma, and are associated with poorer survival on chemotherapy hence these patients may benefit from trial referral (Javle et al. 2016; Montal et al. 2020; Fernandes et al. 2015).

Conclusion

Chemotherapy is currently the standard therapy for advanced cholangiocarcinoma, and some patients will benefit from this. It is important patients who have MSI-H cholangiocarcinoma or targetable mutations as they may respond better to alternate treatments, especially beyond the first-line setting. While these advances are promising, molecular testing and matching agents (including those mentioned above) are often difficult to access outside of a trial.

Key Take Home Messages

1. Outcomes are poor with curative resection alone.
2. Hence adjuvant chemo(radiotherapy) should be considered in all appropriate patients with R1 or node positive disease, but the data is not robust.
3. Chemotherapy is currently the standard of care for unresectable/metastatic disease.
4. Patients with MSI-H disease or targetable mutations may benefit from immunotherapy and targeted therapy.
5. Access to molecular testing, and access to immunotherapy and targeted therapy is a significant barrier.

References

Abou-Alfa, G.K., Sahai, V., Hollebecque, A. et al. (2020). Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 21 (5): 671–684.

Abou-Alfa, G.K., Sahai, V., Hollebecque, A. et al. (2021). Pemigatinib for previously treated locally advanced/metastatic cholangiocarcinoma (CCA): update of FIGHT-202. *J Clin Oncol* 39 (15_suppl): 4086.

André, T., Tournigand, C., Rosmorduc, O. et al. (2004). Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol* 15 (9): 1339–1343.

Bekaii-Saab, T.S., Valle, J.W., Van Cutsem, E. et al. (2020). FIGHT-302: first-line pemigatinib vs gemcitabine plus cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements. *Future Oncol (London, England)* 16 (30): 2385–2399.

Bonneville, R., Krook, M.A., Kautto, E.A. et al. (2017). Landscape of microsatellite instability across 39 cancer types. *JCO Precis Oncol* 1: 1–15.

Chen, J.S., Jan, Y.Y., Lin, Y.C. et al. (1998). Weekly 24 h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract carcinomas. *Anticancer Drugs* 9 (5): 393–397.

Choi, C.W., Choi, I.K., Seo, J.H. et al. (2000). Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. *Am J Clin Oncol* 23 (4): 425–428.

Churi, C.R., Shroff, R., Wang, Y. et al. (2014). Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One* 9 (12): e115383.

Demols, A., Borbath, I., Van den Eynde, M. et al. (2020). Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial. *Ann Oncol* 31 (9): 1169–1177.

Edeline, J., Benabdelghani, M., Bertaut, A. et al. (2019). Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. *J Clin Oncol: Official J Am Soc Clin Oncol* 37 (8): 658–667.

Fernandes, V.T.O., Silva, M.J.D.B.E., Begnami, M.D., and Saito, A. (2015). Prognosis of HER2 expression in cholangiocarcinoma when evaluated using gastric cancer methodology of immunohistochemistry. *J Clin Oncol* 33 (15_suppl): e15203–e.

ClinicalTrials.gov. (2022). Gemcitabine, Cisplatin, and Nab-Paclitaxel Before Surgery in Patients With High-Risk Liver Bile Duct Cancer. Full Text View.

Guion-Dusserre, J.F., Lorgis, V., Vincent, J. et al. (2015). FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma. *World J Gastroenterol* 21 (7): 2096–2101.

Ikeda, M., Nakachi, K., Konishi, M. et al. (2022). Adjuvant S-1 versus observation in curatively resected biliary tract cancer: a phase III trial (JCOG1202: ASCOT). *J Clin Oncol* 40 (4_suppl): 382.

Javle, M., Bekaii-Saab, T., Jain, A. et al. (2016). Biliary cancer: utility of next-generation sequencing for clinical management. *Cancer* 122 (24): 3838–3847.

Javle, M., Churi, C., Kang, H.C. et al. (2015). HER2/neu-directed therapy for biliary tract cancer. *J Hematol Oncol* 8: 58.

Kato, A., Shimizu, H., Ohtsuka, M. et al. (2013). Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. *Ann Surg Oncol* 20 (1): 318–324.

Kim, S.T., Kang, J.H., Lee, J. et al. (2019). Capecitabine plus oxaliplatin versus gemcitabine plus oxaliplatin as first-line therapy for advanced biliary tract cancers: a multicenter, open-label, randomized, phase III, noninferiority trial. *Ann Oncol* 30 (5): 788–795.

Klein, O., Kee, D., Nagrial, A. et al. (2020). Evaluation of combination nivolumab and ipilimumab immunotherapy in patients with advanced biliary tract cancers: subgroup analysis of a phase 2 nonrandomized clinical trial. *JAMA Oncol* 6 (9): 1405–1409.

Lamarca, A., Palmer, D.H., Wasan, H.S. et al. (2021). Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 22 (5): 690–701.

Le Roy, B., Gelli, M., Pittau, G. et al. (2017). Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg* 105 (7): 839–847.

Lowery, M.A., Ptashkin, R., Jordan, E. et al. (2018). Comprehensive Molecular Profiling of Intrahepatic and Extrahepatic Cholangiocarcinomas: potential Targets for Intervention. *Clin Cancer Res* 24 (17): 4154–4161.

Makawita, S., Roychowdhury, G.K.-A.-A., Sadeghi, S. et al. (2020). Infigratinib in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF 301 trial. *Future Oncol (London, England)* 16 (30): 2375–2384.

Marabelle, A., Le, D.T., Ascierto, P.A. et al. (2020). Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol: Official J Am Soc Clin Oncol* 38 (1): 1–10.

Montal, R., Sia, D., Montironi, C. et al. (2020). Molecular classification and therapeutic targets in extrahepatic cholangiocarcinoma. *J Hepatol* 73 (2): 315–327.

Nakamura, H., Arai, Y., Totoki, Y. et al. (2015). Genomic spectra of biliary tract cancer. *Nat Genet* 47 (9): 1003–1010.

ClinicalTrials.gov. (2020). Neoadjuvant Gemcitabine Plus Cisplatin With or Without Durvalumab in Resectable Biliary Tract Cancer. Full Text View.

Neoptolemos, J.P., Moore, M.J., Cox, T.F. et al. (2012). Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *Jama* 308 (2): 147–156.

Novarino, A.M., Satolli, M.A., Chiappino, I. et al. (2013). FOLFOX-4 regimen or single-agent gemcitabine as first-line chemotherapy in advanced biliary tract cancer. *Am J Clin Oncol* 36 (5): 466–471.

Oh, D.-Y., Lee, K.-H., Lee, D.-W. et al. (2020). Phase II study assessing tolerability, efficacy, and biomarkers for durvalumab (D) ± tremelimumab (T) and gemcitabine/cisplatin (GemCis) in chemo-naïve advanced biliary tract cancer (aBTC). *J Clin Oncol* 38 (15_suppl): 4520-.

Okusaka, T., Nakachi, K., Fukutomi, A. et al. (2010). Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 103 (4): 469–474.

Patt, Y.Z., Hassan, M.M., Aguayo, A. et al. (2004). Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. *Cancer* 101 (3): 578–586.

Penz, M., Kornek, G.V., Raderer, M. et al. (2001). Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. *Ann Oncol* 12 (2): 183–186.

Phelip, J., Desrame, J., Edeline, J. et al. (2022). Modified FOLFIRINOX versus CISGEM chemotherapy for patients with advanced biliary tract cancer (PRODIGE 38 AMEBICA): a randomized phase II study. *J Clin Oncol* 40 (3): 262–271.

Piha-Paul, S.A., Oh, D.Y., Ueno, M. et al. (2020). Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. *Int J Cancer* 147 (8): 2190–2198.

Primrose, J.N., Fox, R.P., Palmer, D.H. et al. (2019). Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 20 (5): 663–673.

Rizzo, A. and Brandi, G. (2021). Neoadjuvant therapy for cholangiocarcinoma: a comprehensive literature review. *Cancer Treat Res Commun* 27: 100354.

Sahai, V., Catalano, P.J., Zalupski, M.M. et al. (2018). Nab-paclitaxel and gemcitabine as first-line treatment of advanced or metastatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol* 4 (12): 1707–1712.

Sasaki, T., Isayama, H., Nakai, Y. et al. (2013). A randomized phase II study of gemcitabine and S-1 combination therapy versus gemcitabine monotherapy for advanced biliary tract cancer. *Cancer Chemother Pharmacol* 71 (4): 973–979.

Shroff, R.T., Javle, M.M., Xiao, L. et al. (2019). Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: a phase 2 clinical trial. *JAMA Oncol* 5 (6): 824–830.

Shroff, R.T., Kennedy, E.B., Bachini, M. et al. (2019). Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. *J Clin Oncol* 37 (12): 1015–1027.

Subbiah, V., Lassen, U., Élez, E. et al. (2020). Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 21 (9): 1234–1243.

Valle, J., Wasan, H., Palmer, D.H. et al. (2010). Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 362 (14): 1273–1281.

Valle, J.W., Borbath, I., Khan, S.A. et al. (2016). Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27 (suppl 5): v28–v37.

Verlingue, L., Malka, D., Allorant, A. et al. (2017). Precision medicine for patients with advanced biliary tract cancers: an effective strategy within the prospective MOSCATO-01 trial. *Eur J Cancer* 87: 122–130.

Yoo, C., Kim, K.P., Jeong, J.H. et al. (2021). Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *Lancet Oncol* 22 (11): 1560–1572.

Zhu, A.X., Meyerhardt, J.A., Blaszkowsky, L.S. et al. (2010). Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 11 (1): 48–54.

Zou, S., Li, J., Zhou, H. et al. (2014). Mutational landscape of intrahepatic cholangiocarcinoma. *Nat Commun* 5 (1): 5696.

Radiation Therapy

Natalie Collier

Unresectable Intrahepatic Cholangiocarcinoma (Icca)

Up to 70% of patients with non-metastatic unresectable iCCA experience first progression in the primary tumour despite palliative chemotherapy, and overall survival remains poor. Only recently, external beam radiation therapy (EBRT) has been recommended in guidelines for unresectable iCCA after induction chemotherapy; or alone for those unsuitable for induction chemotherapy (Apisarnthanarax et al. 2022). EBRT may reduce the occurrence of liver failure and death, current recommendations for definitive RT are based on retrospective and phase I/II data.

Dose Escalation

There has been a strong signal from retrospective and prospective studies, that a relationship exists between RT dose and increasing iCCA tumour control (Hong et al. 2016; Tao et al. 2016). Tao et al. (2016) demonstrated that dose escalation to ablative doses compared to lower doses resulted in improved local control (78% vs 45%, P=0.04) and overall survival (73% vs 38%, P=0.017) at 3 years. (Hong et al. 2016; Tao et al. 2016) reported a high 2-year local control rate of 94.1%, with local recurrences occurring solely in the lower radiation dose group.

A Biological Equivalent Dose (BED) > 80.5Gy appears to be ablative for iCCA and can be achieved with various regimens (Table 6). There is no randomised data comparing prescription doses and fractionation schedules, and therefore selection should be based on risk of toxicity to organs-at-risk (OARs), and available techniques (discussed below).

Table 6 Radiotherapy regimens with ablative potential in iCCA treatment[1].

Type of fractionation regimen	Dose per fraction (Gy/#)	Typical number of fractions	Example of regimen with ablative potential
Conventional fractionation (CFx)	1.8–2	25–30	n/a Non-ablative CFx regimen = 50Gy/25#
Moderate hypofractionation (MHFx)	3–5	12–20	58–67.5Gy/15# (4.5Gy per #)
Ultra-hypofractionation (UHFx)	>5	≤10	51Gy/6#
Stereotactic Body Radiation Therapy (SBRT)	>5	≤5	45-50Gy/5#

[1] Biological Equivalent Dose (BED) > 80.5Gy.

Radiotherapy Technique

Large targets, and those adjacent to critical normal structures are challenging to treat. Modern techniques incorporating highly conformal radiotherapy, patient immobilisation, assessment/management of tumour motion and image guidance during treatment delivery are important and are incorporated in prospective trial protocols (NCT02200042 (NRG Oncology 2017)).

Options for precise radiotherapy delivery, include megavoltage photons or charged particles (e.g. protons), and choice of technology is largely dependent on availability. Protons have a unique advantage, which may correlate to a clinical benefit by enabling dose escalation and OAR-sparing, with no exiting dose. Delivery of internal radiotherapy with brachytherapy has also be utilised in a number of settings to dose-escalate (discussed previously).

A phase II study (Hong et al. 2016) for unresectable or locally recurrent iCCA with a median tumour size of 6cm (range 2.2–10.9cm), used protons to deliver 58.05–67.5Gy/15#, with an excellent 2-year local control and overall survival rates of 94.1% and 46.5%, with 7.7% of patients experiencing grade 3 toxicity.

Hepatobiliary Toxicity (HBT)

Caution has been exerted for many years over radiation to the liver. Through increasing awareness of liver tolerance to RT, reducing low-moderate doses to normal liver and using modern RT techniques, the risk of radiation-induced liver disease (RILD) can be minimised. Other factors which may increase the risk of RILD include underlying cirrhosis, liver impairment, prior/concurrent systemic therapy, and tumour size (Pan et al. 2010).

A Phase I Stereotactic Body Radiation Therapy (SBRT) study (Tse et al. 2008) first reported acute temporary biliary obstruction, in 2 out of 10 patients with iCCA; likely from tumour oedema due to ultra-hypofractionation. (Osmundson et al. 2015) defined factors that predicted HBT after SBRT for primary and metastatic liver tumours. There was a significant relationship between grade ≥3 toxicity and dose to the central hepatobiliary tract, and recommended dose constraints have since been published (Toesca et al. 2017).

Clearly ablative doses for disease control need to be balanced with the risk of HBT, and some trials have adopted a modified dose based on tumour location. A phase II study prescribed 67.5Gy/15# for peripheral tumours, and 58.05Gy/15# to tumours <2cm from the porta hepatis, resulting in acceptable rates of grade 3 toxicity for patients with iCCA (7.7%) and no grade 4/5 events.

Randomised Phase III Trials

The NRG-GI001 Randomised phase III attempted to randomised 146 patients with unresectable localised iCCA and no tumour progression following induction gemcitabine/cisplatin chemotherapy, to either radiation therapy or observation (see Table 7 for eligibility criteria) (NRG Oncology 2017). Use of

Table 7 Eligibility criteria for the NRG-GI001 randomised phase III study of focal radiation therapy for unresectable localised iCCA (NCT02200042).

	Criteria
1	Pathological diagnosis of iCCA without distant extrahepatic metastasis.
2	Single lesion with a maximum axial diameter of 12cm at the time of study entry. Up to 3 satellite lesions (less than 2 cm that are within 1 cm of the periphery of the dominant lesion) are permitted. Clinically positive regional porta hepatis lymph nodes are permitted.
3	CT scan chest/abdomen/pelvis with multiphasic liver CT scan within 30 days prior to study entry (or CT chest without contrast plus MRI of abdomen/pelvis)
4	Zubrod Performance Status 0–1
5	Age ≥ 18;
6	Adequate bone marrow and organ function: • Absolute neutrophil count (ANC) ≥ 1,000 cells/mm; • Platelets ≥ 75,000 cells/mm^3; Total bilirubin < 2.5 mg/dl; • AST and ALT < 5.0 X institutional upper limit of normal; • Albumin ≥ 2.5 mg/dl; • Creatinine within normal institutional limits or creatinine clearance ≥ 60mL/min/1.73 m2 • Hemoglobin ≥ 9.0 g/dl.
7	Must have received 6 months of Gemcitabine/Cisplatin chemotherapy without progression (or at least 4 months if toxicity precludes 6 months).

image-guidance and real-time RT quality assurance was mandated, and the highest dose deliverable in 15# was 67.5Gy; modified to prioritise the mean dose constraint to the liver and GI luminal structures. Unfortunately, the study closed early due to unmet accrual goals, and no outcome data is expected.

A second randomised trial (NCT02773485) comparing 52.5-60Gy/25# using modern RT with weekly gemcitabine and 8 cycles of cisplatin and gemcitabine, to 8 cycles of chemotherapy alone for non-metastatic unresectable CCA (iCCA and eCCA), has an estimated completion in mid-2022.

Concurrent Chemotherapy with Definitive RT

There are potential advantages of using radio-sensitising chemotherapy with radiotherapy, particularly if ablative doses cannot be achieved, although there is no standard regimen or recommendation for use. The choice of agent should be based on individual patient factors.

Conventionally fractionated radiotherapy to a dose of 50-60Gy with fluoropyrimidine-based chemotherapy is included in recent guidelines (NCCN 2022). Concurrent chemotherapy with ultra-hypofractionation/SBRT is not considered common or safe practice and is not included in guideline recommendations.

Unresectable Extrahepatic Cholangiocarcinoma

Radiotherapy fields for eCCA are more likely to abut or overlap sensitive OARs and there are valid concerns about the use of ablative doses in this location. In the absence of safety data to support the use of dose-escalation or moderate/ultra-hypofractionation for extrahepatic tumours, conventionally fractionated radiotherapy up to 60Gy with fluoropyrimidine-based chemotherapy is considered acceptable (NCCN 2022).

A randomised phase 2 trial by (Phelip et al. 2014) closed early due to slow recruitment, and although no significant conclusions were made, the results suggest that PFS and OS with CRT (50Gy with 5-FU and cisplatin) alone may not be adequate without additional standard chemotherapy. However, the rate of biliary complications appeared less frequent on the CRT arm compared to 6 months of CT alone (28% vs 44% (risk ratio (RR): 1.60 [0.65–3.92])). The results of the recruiting phase III study (NCT02773485) for unresectable CCA (including eCCA) discussed in the randomised trials section, are anticipated (CRT 60Gy/25# + CT, compared to CT alone).

The outcomes of phase I/II trials investigating dose-escalation are awaited. The STRONG phase I trial (n=6) (NCT03307538), completed in January 2021, used risk-adapted doses up to 67.5Gy/15# for peri-hilar tumours using stereotactic techniques, following standard chemotherapy (Koedijk et al. 2018). The UK ABC-07 phase II trial (ISRCTN10639376) continues to recruit and deliver moderately or ultra-hypofractionated radiotherapy to unresectable eCCA or iCCA following chemotherapy.

Palliative Radiotherapy Following Biliary Stenting

(Shinohara et al. 2009) concluded that patients who received palliative RT in the SEER database, had an improved survival compared to no RT or surgery, though this was a heterogenous group with no information about biliary stenting. Approaches to delay tumour progression causing biliary stent re-occlusion, aside from EBRT, have included intra-luminal brachytherapy (ILBT) or radioactive stents (see earlier section).

Those who survive long enough, remain at risk of toxicity from high radiation doses, and the optimal RT schedule, when the primary goal is to palliate symptoms and prevent stent re-occlusion, is not defined. Several recent series have reported safety and efficacy of EBRT following stent insertion, including a retrospective comparison of 25 patients who received 37–40.7Gy/10–11# after percutaneous biliary stenting (PBS), to 13 patients with PBS alone. There were significant improvements in median stent patency (326d vs 196d) and median overall survival (12.2m vs 8.9m), with no difference in early complication rates (Tan et al. 2015).

Adjuvant Chemoradiotherapy

Multi-disciplinary discussion around reducing the risk of recurrence is recommended, particularly for patients with high risk features including positive surgical margin (R1) and lymph node positivity. Despite the increasing use of liver radiotherapy, there is still no standard adjuvant approach for resected CCA (Table 8).

Resected eCCA

Non-randomised phase 2 trials and meta-analyses support the efficacy of adjuvant CRT, with the most benefit seen in LN positive and R1 resections. The SWOG S0809 phase 2 trial for resected T2-4 R0, R1 or pN+ eCCA and GBC reported promising 2-year OS outcomes of 76% for R0 and 60% for R1 resections, with adjuvant capecitabine and gemcitabine, followed by CRT (45–59.4Gy/25# with capecitabine). Some retrospective studies have escalated doses by using either intra-operative radiotherapy (IORT) or brachytherapy, though the benefit in this cohort is not clear.

A sub-study of the currently recruiting randomised phase 3 ACTICCA-1 study (NCT02170090), randomises eligible patients with R1 resected iCCA, eCCA or pCCA between gemcitabine/cisplatin or capecitabine for 24 weeks, or 18 weeks followed by concurrent CRT with capecitabine. Lymph node positive R0 resections are excluded.

Table 8 Meta-analyses on adjuvant radiotherapy in eCCA.

Study	Patient cohort	Comparison	No. studies	Outcome	Other
(Beltrán et al., 2012)	eCCA, GBC and ampullary cancer	Adjuvant RT or CRT with 5FU vs surgery alone	10	Improved OS (HR 0.62, 95% CI: 0.48–0.78)	Late toxicity 2–9%, mainly GIB or late obstruction
(Horgan et al. 2012)	CCA and GBC (25%)	Adjuvant CT, RT or CRT vs surgery alone	20	Improved OS with CT (OR 0.39, 95% CI: 0.23–0.66) and CRT (OR 0.61, 95% CI: 0.38–0.99) but not RT alone	Most benefit for LN positive and R1 resection.
(Ren et al. 2020)	eCCA and GBC	Adjuvant RT or CRT vs surgery alone	21	Improved 5-year OS rate (OR0.63, 95% CI: 0.50–0.81),	Most benefit for LN positive and R1 resection, NS benefit for R0

eCCA: extra-hepatic cholangiocarcinoma, GBC: gall bladder cancer, OS: overall survival, GIB: gastrointestinal bleed, LN: lymph node, R1: positive resection margin.

Resected iCCA

Retrospective data suggests a benefit to post-operative radiotherapy for lymph node positive and R1 resections, though higher quality data is awaited (see previous). Retrospective evaluation of definitive iCCA treatment in the SEER database (Shinohara et al. 2008), revealed that surgery and adjuvant RT conferred a significant benefit on OS compared to surgery alone. The retrospective nature, lack of concurrent/adjuvant chemotherapy information, and absence of patient specific limits this analysis.

In an evaluation of 70 patients with iCCA adherent to major vessels, the outcomes of patients with narrow margin resection (70%), defined as <1.0cm (47–51% R1), were compared to margins of ≥1.0cm (Zheng et al. 2018). In the narrow-margin group, 50% received adjuvant radiotherapy (no CT), with 3-year OS/PFS rates similar to wide-margin resections, compared to poorer outcomes for narrow-margins. Furthermore, a review of 137 patients (58% iCCA, 25% LN+) who received surgery ± adjuvant therapy (53%) with CT, CRT or RT, demonstrated that adjuvant CRT (10%) was seen to improve RFS compared to surgery alone (Kim et al. 2017).

Key Take Home Messages

1. Definitive EBRT for inoperable localised cholangiocarcinoma (CCA) ± induction chemotherapy may reduce liver failure and death
2. Conventionally fractionated regimens (e.g. 50.4Gy/28#) ± concurrent chemotherapy appear to be well-tolerated
3. EBRT alone to "ablative doses" for intrahepatic CCA can be achieved with modern techniques and hypofractionation (> 2Gy/fraction), with high local control rates
4. Multi-disciplinary discussion around reducing recurrence after surgery should include chemoradiotherapy, particularly for high risk patients (R1, lymph node positive)
5. Liver radiation therapy should always be balanced with the risk of toxicity and the goals of care
6. High-level evidence to support RT for CCA is not yet available, and randomised studies are awaited

References

Apisarnthanarax, S., Barry, A., Cao, M. et al. (2022). External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. *Pract Radiat Oncol* 12: 28–51.

Beltrán, M.B., Allal, A.S., Gich, I. et al. (2012). Is adjuvant radiotherapy needed after curative resection of extrahepatic biliary tract cancers? A systematic review with a meta-analysis of observational studies. *Cancer Treat Rev* 38: 111–119.

Hong, T.S., Wo, J.Y., Yeap, B.Y. et al. (2016). Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 34: 460.

Horgan, A.M., Amir, E., Walter, T., and Knox, J.J. (2012). Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*.

Kim, Y.S., Oh, S.Y., Go, S.-I. et al. (2017). The role of adjuvant therapy after R0 resection for patients with intrahepatic and perihilar cholangiocarcinomas. *Cancer Chemother Pharmacol* 79: 99–106.

Koedijk, M.S., Heijmen, B.J., Koerkamp, B.G. et al. (2018). Protocol for the STRONG trial: stereotactic body radiation therapy following chemotherapy for unresectable perihilar cholangiocarcinoma, a phase I feasibility study. *BMJ open* 8: e020731.

NCCN. (2022). Hepatobiliary Cancers. *NCCN Guidelines*, Version 1.2022.

Oncology, N. (2017). Randomized phase III study of focal radiation therapy for unresectable, localized intrahepatic cholangiocarcinoma. *NRG-GI001*.

Osmundson, E.C., Wu, Y., Luxton, G. et al. (2015). Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. *Int J Radiat Oncol Biol Phys* 91: 986–994.

Pan, C.C., Kavanagh, B.D., Dawson, L.A. et al. (2010). Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys* 76: S94–S100.

Phelip, J.-M., Vendrely, V., Rostain, F. et al. (2014). Gemcitabine plus cisplatin versus chemoradiotherapy in locally advanced biliary tract cancer: Fédération Francophone de Cancérologie Digestive 9902 phase II randomised study. *Eur J Cancer* 50: 2975–2982.

Ren, B., Guo, Q., Yang, Y. et al. (2020). A meta-analysis of the efficacy of postoperative adjuvant radiotherapy versus no radiotherapy for extrahepatic cholangiocarcinoma and gallbladder carcinoma. *Radiat Oncol* 15: 1–10.

Shinohara, E.T., Mitra, N., Guo, M., and Metz, J.M. (2008). Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 72: 1495–1501.

Shinohara, E.T., Mitra, N., Guo, M., and Metz, J.M. (2009). Radiotherapy is associated with improved survival in adjuvant and palliative treatment of extrahepatic cholangiocarcinomas. *Int J Radiat Oncol Biol Phys* 74: 1191–1198.

Tan, Y., Zhu, J.Y., Qiu, B.A. et al. (2015). Percutaneous biliary stenting combined with radiotherapy as a treatment for unresectable hilar cholangiocarcinoma. *Oncol Lett* 10: 2537–2542.

Tao, R., Krishnan, S., Bhosale, P.R. et al. (2016). Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. *J Clin Oncol* 34: 219.

Toesca, D.A., Osmundson, E.C., Von Eyben, R. et al. (2017). Central liver toxicity after SBRT: an expanded analysis and predictive nomogram. *Radiother Oncol* 122: 130–136.

Tse, R.V., Hawkins, M., Lockwood, G. et al. (2008). Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 26: 657–664.

Zheng, X., Chen, B., Wu, J.-X. et al. (2018). Benefit of adjuvant radiotherapy following narrow-margin hepatectomy in patients with intrahepatic cholangiocarcinoma that adhere to major vessels. *Cancer Manag Res* 10: 3973.

Other Therapies

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Biliary Drainage for Cholangiocarcinoma

In the setting of malignant biliary obstruction, drainage improves mortality (Liang et al. 2021). The strategy for drainage in malignant biliary obstruction depends on both stricture location and whether treatment is with palliative or curative intent. This creates a complicated set of decision permutations which outlined below and in Table 9.

Distal Biliary Strictures

Drainage of dCCA strictures is by stent placement at ERCP (Scatimburgo et al. 2021). If ERCP is unsuccessful or infeasible, alternative approaches including percutaneous or EUS-guided drainage may be employed (Hayat et al. 2022).

Advantages and disadvantages of different stent types are well addressed in the pancreatic cancer literature (Nehme and Lee 2022). Usually at the index procedure, a pathological diagnosis of malignancy has not yet been made. To allow neoadjuvant chemotherapy or as a “bridge-to-surgery”, removable plastic or fully-covered self-expanding metal stent (SEMS) are preferred. The role for perioperative biliary drainage is addressed above. Definitive palliative stenting is best performed with uncovered SEMS, which do not require routine replacement, and have a low risk of stent migration. Tumour ingrowth may occur, hence the use in certain situations of covered or partially-covered SEMS, which carry the potential higher risk of cholecystitis (Scatimburgo et al. 2021; Yamashita et al. 2022).

Hilar Strictures

Hilar strictures present further challenges, and the management strategy is also dependent on patient and disease factors. Strictures more advanced than Bismuth I preclude complete hepatic drainage with a single stent. In addition, ERCP management of hilar strictures is more technically challenging than distal strictures, meaning some centres favour percutaneous transhepatic biliary drainage (PTBD) depending on local expertise. Care should be taken to not inject contrast into ducts which are not planned for drainage, to reduce the risk of cholangitis. If a definitive diagnosis of malignancy is not made prior to ERCP then removable plastic stents are placed. Covered SEMS are not used for hilar strictures due to the risk of

Table 9 Biliary drainage options in the setting of cholangiocarcinoma.

		Management Intent	
		Curative	**Palliative**
Location of obstruction	Hilar	Plastic biliary stent(s) placed at ERCP, draining future liver remnant as a bridge to surgery	Either endoscopic or percutaneous drainage of at least 30–50% of liver using metal stents
	Distal	Either • Surgery as primary drainage procedure • Endoscopically placed plastic or removeable metal stent as bridge to surgery	Endoscopic drainage, ideally with metal stents

blocking intra-hepatic ductal side branches. For palliative biliary drainage, uncovered SEMS offer the best long-term drainage option. Three randomised controlled trials have shown a lower rate of stent failure and re-intervention compared with plastic stents; one also showing an improvement in survival (H.J. Mukai et al. 2013; Sangchan et al. 2012; Wagner et al. 1993).

Choosing single versus multiple biliary SEMS to improve the volume of liver drained is controversial. Pre-procedural cross-sectional imaging, particularly MRCP, is useful to assess the feasibility of draining multiple biliary segments. The proportion of the liver that needs to be drained to achieve “effective drainage” – defined by resolution of jaundice, has been assessed in uncontrolled (Hintze et al. 2001) and retrospective (Bulajic et al. 2012; Takahashi et al. 2015; Vienne et al. 2010) studies. These suggest that drainage of 33% may be adequate to palliate jaundice, however often 50% is required. Achieving drainage of multiple biliary segments with multiple stents is procedurally more challenging. Several meta-analyses using retrospective data and including other causes of hilar malignant biliary obstruction (MBO), provide disparate conclusions concerning placement of single versus multiple stents. Advocates of bilateral drainage, cite prolonged stent patency and lower rates of reintervention (Ashat et al. 2019; F. Yang et al. 2021). Other studies suggest no difference in effective drainage, with increased complications when multiple SEMS were utilised (Fu et al. 2021; Meybodi et al. 2020). Overall however, in the setting of more complex Bismuth strictures, if preceding cross-sectional imaging confirms multiple SEMS can achieve drainage of the majority of the liver then our group will usually endeavour to place at least two SEMS.

EUS Guided Biliary Drainage

EUS-guided biliary drainage has recently evolved in settings where ERCP has been unsuccessful. In these studies dCCA has been grouped with other causes of distal MBO. The technique involves biliary puncture under EUS guidance, with subsequent placement of a lumen-apposing metal stent creating a choledochoduodenostomy (EUS-CD). Clinical success appears to be equivalent with lower rates of complications compared with PTBD, for patients with distal MBO and failed ERCP (Hayat et al. 2022). Studies have also assessed EUS-CD as the initial procedure as an alternative to ERCP, showing no difference between technical and clinical success, and overall adverse events (Lyu et al. 2021) . A similar technique, EUS-guided hepaticogastrostomy (EUS-HG), has been employed to drain hilar strictures using a trans-gastric approach to puncture the intrahepatic biliary tree and place a stent. EUS-HG and PTBD each share the potential for peritoneal seeding and difficulties in placing multiple stents to achieve adequate liver drainage particularly in the setting of more complex Bismuth strictures. Furthermore, EUS-HG has a higher risk of complications compared to EUS-CD (J. Li et al. 2022).

Intrahepatic Cholangiocarcinoma – Locoregional Therapies

There are limited data concerning the role of locoregional therapies to manage iCCA. Data is usually combined with other intra-hepatic tumours (including hepatocellular carcinoma and metastatic adenocarcinoma). There are no comparative randomised data available. Substantial retrospective data suggest improved overall survival with these approaches compared with historical controls. In these studies, locoregional therapies are used to achieve local control in patients with non-resectable disease, or to treat post-surgical recurrence. Radiofrequency ablation (RFA) and microwave ablation seem to be effective for local control of lesions usually smaller than 3cm (G.H. Kim et al. 2022). Trans-arterial chemoembolization (TACE) and brachytherapy have also been used, but only a few retrospective studies report benefit (Jonczyk et al. 2018; Liu et al. 2020). Many patients receiving locoregional therapies receive additional chemotherapy. Irreversible electroporation has recently been assessed in small pilot studies but remain confined to subspecialist centres.

Endobiliary Radiofrequency Ablation

RFA is a relatively new technique to treat ductal biliary tumours. Tissue necrosis is induced by delivery of thermal energy to tumours either at ERCP (Figure 10) or PTBD. RFA is used in combination with palliative biliary stenting. RFA has also been used in neoadjuvant settings to manage eCCA (E.J. Kim et al. 2018) and for therapy of tumour ingrowth causing occlusion to existing biliary stents (So et al. 2021). To date, six prospective randomised controlled RFA trials have been published. Survival was improved by 4.1–4.9 months in three of the four studies designed to detect this difference (Gao et al. 2021; J. Yang et al. 2018; Hu et al. 2016). The complication rate from RFA, is up to 19% (Alvarez-Sánchez and Napoléon 2016). Most are mild, and take the form of typical ERCP-related complications, however cholecystitis, haemobilia and other vascular complications are more common.

Photodynamic Therapy

Photodynamic therapy (PDT) relies on preferential accumulation of a parenterally administered photosensitising agent (e.g. porfimer sodium or hematoporphyrin) in tumour cells. When light of a specified wavelength is applied, it generates oxygen radicals, ultimately resulting in tumour cell death. PDT has mostly been used in the palliative setting for patients with unresectable biliary malignancy. There are also several studies in the neoadjuvant (A.

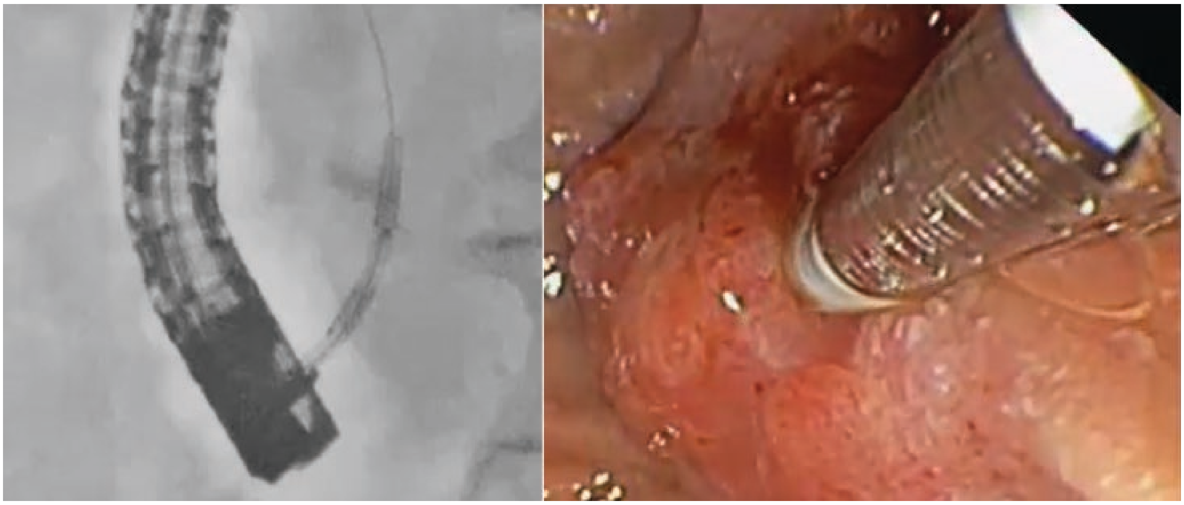

Figure 10 Endobiliary RFA for distal cholangiocarcinoma; fluoroscopy (left), endoscopy (right) demonstrating the RFA probe being inserted into the bile duct.

Wagner et al. 2015), pre-transplant (Cosgrove et al. 2014) and post-surgical recurrence settings (Z. Li et al. 2021).

Several small randomised controlled trials and retrospective analyses assessing PDT in the palliative setting have been reported. Meta-analysis level data suggest that PDT may improve survival, biliary drainage, and performance status (P. Chen et al. 2022). Two RCTs comparing PDT to stenting alone, demonstrated improved survival from 98 to 493 days and 7 to 21 months, respectively (Ortner et al. 2003; Zoepf et al. 2005). The largest and most recent randomised control trial however, was abandoned after it showed overall worse survival in the PDT group – it was not included in the aforementioned meta-analyses. Importantly, PDT has not been widely adopted because it induces cutaneous photosensitivity requiring most patients to avoid direct sunlight for at least 6 weeks.

Brachytherapy

Brachytherapy involves the direct application of a radiation emitting radioisotope to tumours. Rapid dose attenuation results in delivery of high doses of ionising radiation to target CCA, with little exposure of surrounding tissues. High dose rate (HDR) brachytherapy applications involve relatively higher doses administered over short time periods. HDR theoretically has less potential for locoregional toxicities (Mukewar et al. 2015) .

For extrahepatic CCA, HDR brachytherapy with iridium-192 wires has been available for several decades. Its role has been predominantly in the setting of unresectable disease, often administered in parallel with external beam radiotherapy, chemotherapy or other locoregional therapies (Autorino et al. 2020; Bisello et al. 2019). It has also been incorporated into pre-transplant regimens (Mukewar et al. 2015). Delivery is via PTBD or ERCP and modest survival benefits have been observed in retrospective studies (Taggar et al. 2021) and a single randomised controlled trial (Válek et al. 2007). Complications appear to be predominantly related to biliary intervention rather than radiation, however gastroduodenal ulceration and strictures and biliary fistulae, have been reported (Takamura et al. 2003). Delivery of brachytherapy is difficult and, it is not widely used outside the setting of liver transplant.

Low dose rate brachytherapy with iodine-125 "seeds" incorporated into SEMS has been recently studied. Stent placement has usually been via PTBD. In this regard, several randomised controlled trials from China compared conventional SEMS with "radioactive stents". The patient populations included heterogeneous groups with a variety of tumours including small numbers of CCA subjects (Y. Chen et al. 2012; W. Chen et al. 2018; Hasimu et al. 2017; Jiao et al. 2017; Zhu et al. 2012, 2018). These preliminary data were combined in a meta-analysis of all types of malignant biliary obstruction, both distal and hilar, suggesting modest survival benefits (HR 1.6) and stent patency compared with biliary drainage alone (Sha et al. 2021). Complications do not appear increased with brachytherapy seeds compared to conventional SEMS.

Drug-eluting (gemcitabine and cisplatin) stents have also been developed with several small trials and a meta-analysis assessing their use in malignant distal biliary strictures. These studies showed no improvement in either stent patency or patient survival but were associated with increased rates of cholangitis (Yuan et al. 2019).

Key Take Home Messages

1. The majority of eCCA patients with biliary obstruction have unresectable disease and benefit from palliative stenting with a SEMS
2. Technical factors around optimal biliary drainage are complex and often best decided with expert input in a MDT setting
3. In eCCA, endobiliary RFA, and brachytherapy in specific clinical settings are useful adjuncts to biliary stent placement

References

Ali, A.H., Tabibian, J.H., Nasser-Ghodsi, N. et al. (2018 June). Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. *Hepatology (Baltimore, Md)* 67 (6): 2338–2351. https://doi.org/10.1002/hep.29730. https://www.ncbi.nlm.nih.gov/pubmed/29244227 (accessed 19 April 2022).

Alvarez-Sánchez, M.-V. and Napoléon, B. (2016). Review of endoscopic radiofrequency in biliopancreatic tumours with emphasis on clinical benefits, controversies and safety. *World J Gastroenterol* 22 (37): 8257. https://doi.org/10.3748/wjg.v22.i37.8257. http://europepmc.org/articles/pmc5055857?pdf=render (accessed March 2022).

Alvaro, D., Bragazzi, M.C., Benedetti, A. et al. (2011 January). Cholangiocarcinoma in Italy: a national survey on clinical characteristics, diagnostic modalities and treatment. Results from the "Cholangiocarcinoma" committee of the Italian Association for the Study of Liver disease. *Dig Liver Dis* 43 (1): 60–65. https://doi.org/10.1016/j.dld.2010.05.002. https://www.ncbi.nlm.nih.gov/pubmed/20580332 (accessed March 2022).

Arvanitakis, M., Hookey, L., Tessier, G. et al. (2009). Intraductal optical coherence tomography during endoscopic retrograde cholangiopancreatography for investigation of biliary strictures. *Endoscopy* 41 (8). https://doi.org/10.1055/s-0029-1214950. https://www.ncbi.nlm.nih.gov/pubmed/19618343 (accessed April 2022).

Ashat, M., Arora, S., Klair, J.S. et al. (2019). Bilateral vs unilateral placement of metal stents for inoperable high-grade hilar biliary strictures: a systemic review and meta-analysis. *World J Gastroenterol* 25 (34): 5210–5219. https://doi.org/10.3748/wjg.v25.i34.5210.

Autorino, R., Bisiello, S., Pappalardi, B. et al. (2020). Intraluminal Brachytherapy in Unresectable Extrahepatic Biliary Duct Cancer: an Italian Pooled Analysis. *Anticancer Res* 40 (6). https://doi.org/10.21873/anticanres.14326. https://www.ncbi.nlm.nih.gov/pubmed/32487639 (accessed February 2022).

Baison, G.N., Bonds, M.M., Helton, W.S., and Kozarek, R.A. (2019). Choledochal cysts: similarities and differences between Asian and Western countries. *World J Gastroenterol* 25 (26): 3334–3343. https://doi.org/10.3748/wjg.v25.i26.3334. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6639560 (accessed April 2022).

Banales, J.M., Marin, J.J.G., Lamarca, A. et al. (2020). Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 17 (9): 557–588. https://doi.org/10.1038/s41575-020-0310-z.

Bisello, S., Buwenge, M., Palloni, A. et al. (2019). Radiotherapy or chemoradiation in unresectable biliary cancer: a retrospective study. *Anticancer Res* 39 (6): 3095–3100. https://doi.org/10.21873/anticanres.13445.

Bismuth, H. and Corlette, M.B. (1975). Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 140 (2): 170–178.

Boonstra, K., Weersma, R.K., Van Erpecum, K.J. et al. (2013 December). Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 58 (6): 2045–2055. https://doi.org/10.1002/hep.26565.

Bulajic, M., Panic, N., Radunovic, M. et al. (2012). Clinical outcome in patients with hilar malignant strictures type II Bismuth-Corlette treated by minimally invasive unilateral versus bilateral endoscopic biliary drainage. *Hepatobiliary Pancreat Dis Int: HBPD INT* 11 (2). https://doi.org/10.1016/s1499-3872(12)60150-7. https://www.ncbi.nlm.nih.gov/pubmed/22484591 (accessed 15 June 2022).

Chen, L., Lu, Y., Wu, J.C. et al. (2016 February). Diagnostic utility of endoscopic retrograde cholangiography/intraductal ultrasound (ERC/IDUS) in distinguishing malignant from benign bile duct obstruction. *Dig Dis Sci* 61 (2): 610–617. https://doi.org/10.1007/s10620-015-3896-1. https://www.ncbi.nlm.nih.gov/pubmed/26423079 (accessed 30 March 2022).

Chen, M.F., Jan, Y.Y., Wang, C.S. et al. (1993 April 15). A reappraisal of cholangiocarcinoma in patient with hepatolithiasis. *Cancer* 71 (8): 2461–2465. https://doi.org/10.1002/1097-0142(19930415)71:8<2461::aid-cncr2820710806>3.0.co;2-7 https://www.ncbi.nlm.nih.gov/pubmed/8384069 (accessed 19 May 2022).

Chen, P., Yang, T., Shi, P. et al. (2022). Benefits and safety of photodynamic therapy in patients with hilar cholangiocarcinoma: a meta-analysis. *Photodiagnosis Photodyn Ther* 37. https://doi.org/10.1016/j.pdpdt.2022.102712. https://www.ncbi.nlm.nih.gov/pubmed/34995788.

Chen, W., Fang, X.M., Wang, X. et al. (2018). Preliminary clinical application of integrated 125I seeds stents in the therapy of malignant lower biliary tract obstruction. *J X-ray Sci Technol* 26 (5). https://doi.org/10.3233/XST-180403. https://www.ncbi.nlm.nih.gov/pubmed/30040791 (accessed 30 April 2022).

Chen, Y., Wang, X.L., Yan, Z.P. et al. (2012). The use of ^{125}I seed strands for intraluminal brachytherapy of malignant obstructive jaundice. *Cancer Biother Radiopharm* 27 (5). https://doi.org/10.1089/cbr.2011.0999. https://www.ncbi.nlm.nih.gov/pubmed/21902546 (accessed 30 April 2022).

Cosgrove, N.D., Al-Osaimi, A.M., Sanoff, H.K. et al. (2014). Photodynamic therapy provides local control of cholangiocarcinoma in patients awaiting liver transplantation. *Am J Transplant* 14 (2): 466–471. https://doi.org/10.1111/ajt.12597. https://onlinelibrary.wiley.com/doi/pdf/10.1111/ajt.12597 (accessed 12 April 2022).

DeOliveira, M.L., Cunningham, S.C., Cameron, J.L. et al. (2007). Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 245 (5). https://doi.org/10.1097/01.sla.0000251366.62632.d3. https://www.ncbi.nlm.nih.gov/pubmed/17457168 (accessed 30 April 2022).

Fu, Y.F., Xu, Y.S., Shi, Y.B. et al. (2021). Percutaneous metal stenting for malignant hilar biliary obstruction: a systematic review and meta-analysis of unilateral versus bilateral stenting. *Abdom. Radiol. (New York)* 46 (2). https://doi.org/10.1007/s00261-020-02643-y. https://www.ncbi.nlm.nih.gov/pubmed/32671439.

Gao, D.J., Yang, J.F., Ma, S.R. et al. (2021). Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. *Gastrointest Endosc* 94 (1). https://doi.org/10.1016/j.gie.2020.12.016. https://www.ncbi.nlm.nih.gov/pubmed/33359435 (accessed 9 March 2022).

Garcea, G., Ngu, W., Neal, C.P. et al. (2011 June). Bilirubin levels predict malignancy in patients with obstructive jaundice. *HPB* 13 (6): 426–430. https://doi.org/10.1111/j.1477-2574.2011.00312.x. http://europepmc.org/articles/pmc3103100?pdf=render (accessed 30 March 2022).

Gleeson, F.C., Rajan, E., Levy, M.J. et al. (2008 March). EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. *Gastrointest Endosc* 67 (3): 438–443. https://doi.org/10.1016/j.gie.2007.07.018. https://www.ncbi.nlm.nih.gov/pubmed/18061597 (accessed 20 April 2022).

Hasimu, A., Gu, J.P., Ji, W.Z. et al. (2017). Comparative study of percutaneous transhepatic biliary stent placement with or without iodine-125 seeds for treating patients with malignant biliary obstruction. *J Vasc Interv Radiol: JVIR* 28 (4). https://doi.org/10.1016/j.jvir.2016.11.038. https://www.ncbi.nlm.nih.gov/pubmed/28162906 (accessed 30 April 2022).

Hayat, U., Bakker, C., Dirweesh, A. et al. (2022). EUS-guided versus percutaneous transhepatic cholangiography biliary drainage for obstructed distal malignant biliary strictures in patients who have failed endoscopic retrograde cholangiopancreatography: a systematic review and meta-analysis. *Endoscopic Ultrasound* 11 (1). https://doi.org/10.4103/EUS-D-21-00009. https://www.ncbi.nlm.nih.gov/pubmed/35083977 (accessed 8 June 2022).

Heimbach, J.K., Sanchez, W., Rosen, C.B., and Gores, G.J. (2011 May). Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *HPB* 13 (5): 356–360. https://doi.org/10.1111/j.1477-2574.2011.00298.x. http://europepmc.org/articles/pmc3093648?pdf=render (accessed 30 March 2022).

Heinzow, H.S., Kammerer S., Rammes, C. et al. (2014 August 14). Comparative analysis of ERCP, IDUS, EUS and CT in predicting malignant bile duct strictures. *World J Gastroenterol* 20 (30): 10495–10503. https://doi.org/10.3748/wjg.v20.i30.10495. http://resolver.sub.uni-goettingen.de/purl?gs-1/14456 (accessed 30 March 2022).

Hintze, R.E., Abou-Rebyeh, H., Adler, A. et al. (2001). Magnetic resonance cholangiopancreatography-guided unilateral endoscopic stent placement for Klatskin tumors. *Gastrointest Endosc* 53 (1). https://doi.org/10.1067/mge.2001.111388 https://www.ncbi.nlm.nih.gov/pubmed/11154487 (accessed 15 June 2022).

Hu, B., Gao, D.-J., Zhang, X., and Zhang, Y.-C. (2016). 121 endobiliary radiofrequency ablation improve overall survival of cholangiocarcinoma: a multi-center randomized control study. *Gastrointest Endosc* 83 (5). https://doi.org/10.1016/j.gie.2016.03.046. http://www.giejournal.org/article/S0016510716003072/abstract. http://www.giejournal.org/article/S0016510716003072/fulltext. http://www.giejournal.org/article/S0016510716003072/pdf.

Jiao, D., Wu, G., Ren, J., and Han, X. (2017). Study of self-expandable metallic stent placement intraluminal 125 I seed strands brachytherapy of malignant biliary obstruction. *Surg Endosc* 31 (12). https://doi.org/10.1007/s00464-017-5481-5. https://www.ncbi.nlm.nih.gov/pubmed/28643064 (accessed 30 April 2022).

Jonczyk, M., Collettini, F., Schnapauff, D. et al. (2018). Cholangiocarcinoma: CT-guided high-dose rate brachytherapy (CT-HDRBT) for limited (<4 cm) and large (>4 cm) tumors. *Anticancer Res* 38 (10): 5843–5852. https://doi.org/10.21873/anticanres.12926.

Khashab, M.A., Fockens, P., and Al-Haddad, M.A. (2012 November). Utility of EUS in patients with indeterminate biliary strictures and suspected extrahepatic cholangiocarcinoma (with videos). *Gastrointest Endosc* 76 (5): 1024–1033. https://doi.org/10.1016/j.gie.2012.04.451. https://www.ncbi.nlm.nih.gov/pubmed/22749367 (accessed 30 March 2022).

Kim, E.J., Chung, D.H., Kim, Y.J. et al. (2018). Endobiliary radiofrequency ablation for distal extrahepatic cholangiocarcinoma: a clinicopathological study. *PLOS ONE* 13 (11): e0206694. https://doi.org/10.1371/journal.pone.0206694. https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0206694&type=printable (accessed 16 March 2022).

Kim, G.H., Kim, P.H., Kim, J.H. et al. (2022). Thermal ablation in the treatment of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *Eur Radiol* 32 (2): 1205–1215. https://doi.org/10.1007/s00330-021-08216-x.

Krishna, N., Saripalli, S., Safdar, R., and Agarwal, B. (2007 July). Intraductal US in evaluation of biliary strictures without a mass lesion on CT scan or magnetic resonance imaging: significance of focal wall thickening and extrinsic compression at the stricture site. *Gastrointest Endosc* 66 (1): 90–96. https://doi.org/10.1016/j.gie.2006.10.020. https://www.ncbi.nlm.nih.gov/pubmed/17451708 (accessed 30 March 2022).

Li, J., Tang, J., Liu, F., and Fang, J. (2022). Comparison of choledochoduodenostomy and hepaticogastrostomy for EUS-guided biliary drainage: a meta-analysis. *Front Surg* 9. https://doi.org/10.3389/fsurg.2022.811005. https://www.ncbi.nlm.nih.gov/pubmed/35356500.

Li, Z., Jiang, X., Xiao, H. et al. (2021). Long-term results of ERCP- or PTCS-directed photodynamic therapy for unresectable hilar cholangiocarcinoma. *Surg Endosc* 35 (10): 5655–5664. https://doi.org/10.1007/s00464-020-08095-1.

Liang, X.-Y., Wen, L., Liu, F., and Kang, X.-D. (2021). A retrospective study of biliary drainage strategies for patients with malignant hilar biliary strictures. *Cancer Manag Res* 13: 4767–4776. https://doi.org/10.2147/cmar.s308833.

Liu, W.-R., Tian, M.-X., Tao, C.-Y. et al. (2020). Adjuvant Transarterial chemoembolization does not influence recurrence-free or overall survival in patients with combined hepatocellular carcinoma and Cholangio carcinoma after curative resection: a propensity score matching analysis. *BMC Cancer* 20 (1). https://doi.org/10.1186/s12885-020-07138-z.

Lyu, Y., Li, T., Cheng, Y. et al. (2021). Endoscopic ultrasound-guided vs ERCP-guided biliary drainage for malignant biliary obstruction: a up-to-date meta-analysis and systematic review. *Dig Liver Dis* 53 (10). https://doi.org/10.1016/j.dld.2021.03.029. https://www.ncbi.nlm.nih.gov/pubmed/33926814 (accessed 8 June 2022).

Meybodi, A., Mohamad, D.S., Nanavati, J. et al. (2020). Unilateral versus bilateral endoscopic stenting in patients with unresectable malignant hilar obstruction: a systematic review and meta-analysis. *Endosc Int Open* 08 (03): E281–E290. https://doi.org/10.1055/a-1067-4326.

Mukai, T., Yasuda, I., Nakashima, M. et al. (2013). Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. *J Hepatobiliary Pancreat Sci* 20 (2). https://doi.org/10.1007/s00534-012-0508-8. https://www.ncbi.nlm.nih.gov/pubmed/22415652 (accessed 10 April 2022).

Mukewar, S., Gupta, A., Baron, T.H. et al. (2015). Endoscopically inserted nasobiliary catheters for high dose-rate brachytherapy as part of neoadjuvant therapy for perihilar cholangiocarcinoma. *Endoscopy* 47 (10). https://doi.org/10.1055/s-0034-1392044. https://www.ncbi.nlm.nih.gov/pubmed/25961442 (accessed 16 February 2022).

Nehme, F. and Lee, J.H. (2022). Preoperative biliary drainage for pancreatic cancer. *Dig Endosc* 34 (3): 428–438. https://doi.org/10.1111/den.14081.

Ortner, M.E.J., Caca, K., Berr, F. et al. (2003). Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 125 (5): 1355–1363. https://doi.org/10.1016/j.gastro.2003.07.015.

Raine, T., Thomas, J.P., Brais, R. et al. (2020 November). Test performance and predictors of accuracy of endoscopic ultrasound-guided fine-needle aspiration for diagnosing biliary strictures or masses. *Endosc Int Open* 8 (11): E1537–E1544. https://doi.org/10.1055/a-1231-4948.

Reynauld, B., Heng, R., Khabart, M. et al. (2021). Digital single operator cholangioscopy allows accurate diagnosis of most indeterminate biliary strictures. *J Gastroenterol Hepatol* 36 (S3).

Sangchan, A., Kongkasame, W., Pugkhem, A. et al. (2012). Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial. *Gastrointest Endosc* 76 (1). https://doi.org/10.1016/j.gie.2012.02.048. https://www.ncbi.nlm.nih.gov/pubmed/22595446 (accessed 5 April 2022).

Scatimburgo, M., Vieira, V.C., Ribeiro, I.B. et al. (2021). Biliary drainage in inoperable malignant biliary distal obstruction: a systematic review and meta-analysis. *World J Gastrointest Surg* 13 (5): 493–506. https://doi.org/10.4240/wjgs.v13.i5.493.

Scheuermann, U., Widyaningsih, R., Hoppe-Lotichius, M. et al. (2016 May 10). Detection of benign hilar bile duct stenoses - A retrospective analysis in 250 patients with suspicion of Klatskin tumour. *Ann Med Surg (Lond)* 8 (2012): 43–49. https://doi.org/10.1016/j.amsu.2016.05.001. https://www.ncbi.nlm.nih.gov/pubmed/27257485 (accessed 30 March 2022).

Sha, K.H., Liu, T.G., Yang, F. et al. (2021). Irradiation stent insertion for inoperable malignant biliary obstruction: a meta-analysis of randomized controlled trials. *Abdom. Radiol. (New York)* 46 (5). https://doi.org/10.1007/s00261-020-02851-6. https://www.ncbi.nlm.nih.gov/pubmed/33156948 (accessed 30 April 2022).

Slivka, A., Gan, I., Jamidar, P. et al. (2015 February). Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary strictures: results of a prospective multicenter international study. *Gastrointest Endosc* 81 (2): 282–290. https://doi.org/10.1016/j.gie.2014.10.009. https://www.ncbi.nlm.nih.gov/pubmed/25616752 (accessed 30 March 2022).

So, H., Oh, C.H., Song, T.J. et al. (2021). Feasibility and Safety of Endoluminal Radiofrequency Ablation as a Rescue Treatment for Bilateral Metal Stent Obstruction Due to Tumor Ingrowth in the Hilum: a Pilot Study. *J Clin Med* 10 (5): 952. https://doi.org/10.3390/jcm10050952.

Stassen, P.M.C., Goodchild, G., De Jonge, P.J.F. et al. (2021 December). Diagnostic accuracy and interobserver agreement of digital single-operator cholangioscopy for indeterminate biliary strictures. *Gastrointest Endosc* 94 (6): 1059–1068. https://doi.org/10.1016/j.gie.2021.06.027.

Taggar, A.S., Paveen Mann, M.R., Folkert, S.A. et al. (2021). A systematic review of intraluminal high dose rate brachytherapy in the management of malignant biliary tract obstruction and cholangiocarcinoma. *Radiother Oncol* 165: 60–74. https://doi.org/10.1016/j.radonc.2021.10.011.

Takahashi, E., Fukasawa, M., Sato, T. et al. (2015). Biliary drainage strategy of unresectable malignant hilar strictures by computed tomography volumetry. *World J Gastroenterol* 21 (16). https://doi.org/10.3748/wjg.v21.i16.4946. https://www.ncbi.nlm.nih.gov/pubmed/25945008 (accessed 15 June 2022).

Takamura, A., Saito, H., Kamada, T. et al. (2003). Intraluminal low-dose-rate 192Ir brachytherapy combined with external beam radiotherapy and biliary stenting for unresectable extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 57 (5): 1357–1365. https://doi.org/10.1016/s0360-3016(03)00770-3.

Válek, V., Kysela, P., Kala, Z. et al. (2007). Brachytherapy and percutaneous stenting in the treatment of cholangiocarcinoma: a prospective randomised study. *Eur J Radiol* 62 (2). https://doi.org/10.1016/j.ejrad.2007.01.037. https://www.ncbi.nlm.nih.gov/pubmed/17344008 (accessed 13 February 2022).

Vienne, A., Hobeika, E., Gouya, H. et al. (2010). Prediction of drainage effectiveness during endoscopic stenting of malignant hilar strictures: the role of liver volume assessment. *Gastrointest Endosc* 72 (4). https://doi.org/10.1016/j.gie.2010.06.040. https://www.ncbi.nlm.nih.gov/pubmed/20883850 (accessed 10 April 2022).

Wagner, A., Wiedmann, M., Tannapfel, A. et al. (2015). Neoadjuvant downsizing of hilar cholangiocarcinoma with photodynamic therapy—long-term outcome of a phase II pilot study. *Int J Mol Sci* 16 (11): 26619–26628. https://doi.org/10.3390/ijms161125978.

Wagner, H.J., Knyrim, K., Vakil, N., and Klose, K.J. (1993). Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. *Endoscopy* 25 (03): 213–218. https://doi.org/10.1055/s-2007-1010295.

Wen, L.-J., Chen, J.-H., Xu, H.-J. et al. (2020 September 2). Efficacy and safety of digital single-operator cholangioscopy in the diagnosis of indeterminate biliary strictures by targeted biopsies: a systematic review and meta-analysis. *Diagnostics (Basel)* 10 (9): 666. https://doi.org/10.3390/diagnostics10090666.

Yamashita, Y., Tachikawa, A., Shimokawa, T. et al. (2022). Covered versus uncovered metal stent for endoscopic drainage of a malignant distal biliary obstruction: meta-analysis. *Dig Endosc.* https://doi.org/10.1111/den.14260. https://www.ncbi.nlm.nih.gov/pubmed/35114036 (accessed 8 June 2022).

Yang, F., Wang, X.-M., Xia, F.-F., and Han, X.-Q. (2021). REVIEW: endoscopic metal stenting for malignant hilar biliary obstruction: an update meta-analysis of unilateral versus bilateral stenting. *Videosurgery and Other Miniinvasive Techniques* 16 (3): 472–481. https://doi.org/10.5114/wiitm.2021.104196.

Yang, J., Wang, J., Zhou, H. et al. (2018). Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. *Endoscopy* 50 (8). https://doi.org/10.1055/s-0043-124870. https://www.ncbi.nlm.nih.gov/pubmed/29342492 (accessed 16 March 2022).

Yoon, S.B., Moon, S.H., Ko, S.W. et al. (2022 July). Brush cytology, forceps biopsy, or endoscopic ultrasound-guided sampling for diagnosis of bile duct cancer: a meta-analysis. *Dig Dis Sci* 67 (7): 3284–3297. https://doi.org/10.1007/s10620-021-07138-4. https://www.ncbi.nlm.nih.gov/pubmed/34263382 (accessed 29 March 2022).

Yuan, T., Zhu, Y., Wang, X. et al. (2019). Efficacy and safety evaluation of paclitaxel-loaded metal stents in patients with malignant biliary obstructions. *Eur J Surg Oncol* 45 (5). https://doi.org/10.1016/j.ejso.2018.10.533. https://www.ncbi.nlm.nih.gov/pubmed/30389299 (accessed 8 June 2022).

Zhu, H.D., Guo, J.H., Huang, M. et al. (2018). Irradiation stents vs. conventional metal stents for unresectable malignant biliary obstruction: a multicenter trial. *J Hepatol* 68 (5). https://doi.org/10.1016/j.jhep.2017.12.028. https://www.ncbi.nlm.nih.gov/pubmed/29331343 (accessed 30 April 2022).

Zhu, H.D., Guo, J.H., Zhu, G.Y. et al. (2012). A novel biliary stent loaded with (125)I seeds in patients with malignant biliary obstruction: preliminary results versus a conventional biliary stent. *J Hepatol* 56 (5). https://doi.org/10.1016/j.jhep.2011.12.018. https://www.ncbi.nlm.nih.gov/pubmed/22266605 (accessed 30 April 2022).

Zoepf, T., Jakobs, R., Arnold, J.C. et al. (2005). Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 100 (11). https://doi.org/10.1111/j.1572-0241.2005.00318.x. https://www.ncbi.nlm.nih.gov/pubmed/16279895 (accessed 13 April 2022).

22 Management of Cystic Neoplasms of the Pancreas

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Introduction

Pancreatic cystic neoplasms (PCN) encompass a large spectrum of benign, premalignant, and malignant cysts. They are being diagnosed with increasing frequency due to the widespread use of cross-sectional imaging often during work-up for unrelated medical problems (Gardner et al. 2013). The overall risk of a PCN being malignant is low, at less than 0.1% (Scheiman et al. 2015). Despite the increased detection of PCNs, the incidence of pancreatic cancer has remained relatively stable yet there has been a 189% increase in pancreatectomies over the last two decades. Therefore, the tremendous clinical variability of pancreatic cysts presents a significant diagnostic and therapeutic challenge to clinicians. A key component of clinical management of these cysts is to accurately identify the small percentage of cysts with early invasive cancer or high-grade dysplasia and to predict which will develop cancer in the future so as to avoid both missing detection of early cancer and referring for unnecessary surgical intervention (Klibansky et al. 2012; Yoon et al. 2021).

The estimated prevalence of asymptomatic pancreatic cystic neoplasms (PCNs) in the general population is 2.5–15%. Studies have reported high variability in the prevalence of PCNs depending on the imaging modality used, ranging from 2.4% to 44% on magnetic resonance imaging (MRI), to 3% on computed tomography (de Jong et al. 2010; Falqueto et al. 2018; Girometti et al. 2011; Laffan et al. 2008). In one of the largest, population-based studies looking at 25,300 healthy individuals who had an abdominal CT as a part of a health screening exam, the age and sex-adjusted prevalence of PCNs was 2.2% (Chang et al. 2016). In a meta-analysis of 17 studies that included CT and MRI, the global pooled prevalence of PCNs was 8% with the highest prevalence reported in the Americas and in older persons (Zerboni et al. 2019).

Age has been strongly associated with PCN prevalence and it is estimated that 10% of people above 70 years have a pancreatic cyst (Elta et al. 2018). A six-fold increase in the rate of detection has been observed in persons in their eighth decade of life compared to those in their fourth decade of life (Gardner et al. 2013). Moreover, the prevalence, number, and size of cysts have been shown to increase with age. After five years of follow up of participants (mean age of 60.52 years) with PCNs, 30.8% had an increase in size and number of cysts, 24.1% had no change and 1.3% had a reduction in cyst size and number (Kromrey et al. 2018). No difference in prevalence of PCNs by sex have been observed (de Jong et al. 2010; Girometti et al. 2011; Kromrey et al. 2018; Laffan et al. 2008).

The cause of concern when a PCN is detected is the potential for malignant transformation. While the overall risk of malignant transformation for all PCNs remains low (Elta et al. 2018), the risk becomes clinically relevant in mucin producing cystic neoplasms such as intraductal papillary mucinous neoplasm (IPMNs) or mucinous cystic neoplasms (MCNs). In a population-based, cross-sectional analysis comparing the prevalence of mucin-producing adenocarcinomas from the Surveillance Epidemiology and End Results (SEER-18) data to the estimated prevalence of PCNs in the US, the calculated prevalence rate for malignant transformation was rare at 33.2 per 100,000 people (Gardner et al. 2013). However, retrospective studies based on surgical series have estimated a much higher rate of malignancy with a pooled estimate of 15% in resected cysts from an analysis of 1296 patients (Scheiman et al. 2015). In another analysis of 3980 patients with suspected IPMNs, the risk of cancer was reported to be low at 2.8% (Scheiman et al. 2015) but other studies have shown contradictory results. In a systematic review of 99 studies, 42% of the resected IPMNs had either high-grade dysplasia or pancreatic cancer (Scheiman et al. 2015). This significant variability in the reported risk of malignant transformation of PCNs as detailed above is likely due to a large selection bias in these surgical case series and is overestimated which continues to make management decisions challenging. Furthermore, no existing test can identify the type of PCN pre-operatively with a high accuracy. Several guidelines (2015 American Gastroenterological Association [AGA] (Vege et al. 2015), 2016 American Society of Gastrointestinal Endoscopy [ASGE] (Committee, A.S.o.P.

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et al. 2016), 2017 Fukuoka guidelines by International Association of Pancreatology [IAP] (Tanaka et al. 2017), 2018 American College of Gastroenterology [ACG] (Elta et al. 2018), 2018 European Study Group, and American College of Radiology (Elta et al. 2018)) have attempted to risk stratify the PCNs by identifying features that are predictive of harboring malignancy and thus minimizing diagnostic uncertainty that can lead to clinically significant errors for our patients. These features are discussed in detail later in the chapter (Elta et al. 2018; European Study Group on Cystic Tumours of the, P. 2018; Scheiman et al. 2015; Tanaka et al. 2017).

PCNs can be broadly classified as neoplastic versus non-neoplastic and mucin producing versus non-mucin producing. These can be differentiated by cross-sectional imaging and endoscopic ultrasound (EUS) with or without cyst fluid and cyst wall lining analysis though the accuracy of the currently available diagnostic tools to identify the type of PCN remains subpar with advancements in the fields of radiology and endosonography expected to continue to improve upon it (Elta et al. 2018). This chapter will highlight the various types of PCNs (Table 1) and their management but will predominantly focus on the diagnostic and therapeutic management of the mucin producing cystic neoplasms (specifically IPMNs).

Neoplastic and Mucin Producing Pancreatic Cystic Neoplasms

Intraductal Papillary Mucinous Neoplasms

An intraductal papillary mucinous neoplasm (IPMN) can be diagnosed on imaging and is typically connected to the main pancreatic duct; this differentiates IPMNs from mucinous cystic neoplasms (Scheiman et al. 2015). They can be classified by location: side-branch, main duct, or mixed (a combination of side branch and main duct). A branch duct IPMN (BD-IPMN) is the most common PCN and has the lowest risk of harboring high-grade dysplasia and/or invasive cancer (Goh et al. 2014; Nguyen et al. 2015; Sahora et al. 2013). Although some patients with BD-IPMNs warrant consideration for surgical resection, most are incidentally discovered in elderly patients where surveillance is a better option considering the risks associated with surgery and a low annual rate of progression [1.4–6.9%] (Lafemina et al. 2013; Malleo et al. 2015). Mixed and main duct IPMNs are less common but have a higher risk for malignancy with 38–68% of resected main duct IPMNs found to have high-grade dysplasia and/or pancreatic cancer (Elta et al. 2018). Therefore, surgical resection of all IPMNs with suspected main duct involvement is recommended. One interesting endoscopic feature of an MD-IPMN is a fish-eye papilla where a patulous, mucin extruding pancreatic orifice which is visible during duodenoscopy in 20% to 55% of the cases and is more often noted in malignant disease (Elta et al. 2018; Kitagawa et al. 2003; Maire et al. 2003) (Figure 1).

Of note, patients with IPMNs are suspected to have a "field defect" where all ductal epithelial cells in the pancreas are suspected to be at risk for dysplastic change and malignancy. This may be why up to 40% of the patients present with multifocal BD-IPMNs (Rodriguez et al. 2007; Waters et al. 2008) though the cumulative risk of high-grade dysplasia or invasive cancer does not seem to be higher (Tanaka et al. 2017). This is also why it has been noted that patients with BD-IPMNs have an increased risk (around 2–4%) of developing "concomitant" pancreatic adenocarcinoma (PDAC) in an anatomically different area in the pancreatic parenchyma independent to the risk of malignant transformation within the IPMN itself (Maguchi et al. 2011; Tanno et al. 2010). This not only underlines the importance of evaluating the entire pancreas at the time of cyst evaluation but also the need to continue surveillance in the pancreatic remnant after surgical resection of a BD-IPMN or a main duct IPMN. Diagnostic techniques and management of BD-IPMNs is discussed later in the chapter.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) are primarily found in middle aged women in the body or tail of the pancreas. Radiographically, MCNs are round, can be unilocular or multilocular and usually have thick cyst walls. They usually do not communicate with the pancreatic duct and occasionally can have peripheral "eggshell" calcification which is considered a pathognomic feature for MCNs. Histologically, they are distinct from other types of PCNs as they have columnar epithelium surrounded by ovarian stroma. They do have a risk of malignant transformation and in an analysis of resected MCNs high-grade dysplasia or pancreatic cancer, it was demonstrated to be around 10% (Park et al. 2014) though the risk is negligible in MCNs that are smaller than 3 cm in size and have no other concerning radiological characteristics (Goh et al. 2006).

Neoplastic and Non-Mucin Producing Pancreatic Cystic Neoplasms

Serous Cystadenoma

Serous cystadenomas (SCAs) commonly occur in women in their 50s and 60s. They can have three characteristic morphologic appearances on imaging including polycystic, microcystic, or honey combing and oligo-cystic. BD-IPMNs can be differentiated from SCAs based on imaging if the SCA is polycystic or microcystic but this can be challenging if the SCA is oligo-cystic. Another imaging characteristic associated with SCAs is a central calcified scar that can be seen in less than half of these PCNs (Figure 2). The reason why it can be important to differentiate these from mucin producing PCNs is that the risk of malignancy is very low (0.1%) in SCAs and thus surveillance is not generally required. Even though most of these are asymptomatic, occasionally they can cause

		European	AGA	ACG	IAP	ASGE
	Jaundice	Presence of jaundice is considered predictive of malignancy and should be evaluated	Not discussed	Presence of jaundice is considered a high-risk feature and EUS±FNA and/or a multidisciplinary evaluation is recommended	Surgical resection without further testing is recommended in patients presenting with obstructive jaundice worrisome features	Jaundice is a clinical feature associated with ductal adenocarcinoma
	Pancreatitis	Not discussed	Not discussed	Pancreatitis secondary to cyst is considered high-risk	Recommend EUS for further evaluation and consider surgery for symptom relief	History of pancreatitis a clinical feature associated with pseudocysts and IPMNs
Imaging characteristics	**MPD dilation**	≥10 mm dilation is predictive of malignancy	Considered a high-risk feature	>5 mm dilation is considered a high-risk feature and EUS±FNA and/or a multidisciplinary evaluation is recommended	Dilation of 5–9 mm is considered a "worrisome feature".≥10 mm dilation is considered a "high-risk stigma" and surgical resection is recommended	MPD dilation warrants EUS/FNA evaluation
	Mural Nodule	≥5 mm predictive of malignancy	Not discussed	Mural nodule considered a high-risk feature and EUS±FNA and/or a multidisciplinary evaluation is recommended	Considered a "worrisome feature" and an evaluation with EUS is recommended	Presence of a mural nodule warrants EUS/FNA evaluation
	Cyst size	cyst diameter ≥40 mm associated with cancer	≥3 cm cyst size considered a high-risk feature	≥3 cm cyst size considered a high-risk feature and EUS±FNA and/or a multidisciplinary evaluation is recommended	For cysts < 5 mm and no symptoms follow up is recommended. For cysts > 5 mm dedicated imaging is recommended for characterization of cyst	≥3 cm cyst size warrant EUS/FNA
	Pancreatic atrophy	Not discussed	Not discussed	Upstream atrophy considered a high-risk feature and EUS±FNA and/or a multidisciplinary evaluation is recommended	Pancreatic atrophy is considered a "worrisome feature" and EUS is recommended	Not discussed

Serum Based	**CA 19-9**	Can be considered when there is concern for malignancy	Not discussed		If benign causes of elevated CA19-9 are not found, then a multidisciplinary evaluation should be pursued	Considered a “worrisome feature” and EUS is recommended	Not discussed		
	New-onset Diabetes	Relative indication for surgery	Not discussed		Considered a concerning symptom and EUS or MRI should be considered	Not discussed	Not discussed		
Surveillance	**First year of diagnosis**	Clinical evaluation, CA19-9, MRI and/ or EUS every 6 months	**< 3 cm**	MRI for surveillance in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics	**< 1cm**	MRI every 2 years for 4years	**< 1cm**	CT / MRI in 6 months, then every 2 years if no change	
					1-2 cm	MRI every year for 3 years	**1-2 cm**	CT / MRI for 6 months for 1 year, then yearly for 2 years and then every 2 years if stable	
	After the first year of diagnosis	Clinical evaluation, CA19-9, MRI and/ or EUS every year			**2-3 cm**	MRI or EUS every 6–12 months for 3 years	**2-3 cm**	EUS in 3-6 months, followed by alternating MRI with EUS every year. Can consider surgery in young patients	Not discussed
			>3 cm	Recommend examination with EUS-FNA	**>3cm**	Referral to multidisciplinary group and MRI alternating with EUS every 6 months for 3 years	**>3cm**	Close surveillance alternating with MRI with EUS every 3-6 months. Should consider surgery in young patients	

Table 1 Characteristic and epidemiology of different pancreatic cystic neoplasms.

Characteristic	MCN	BD-IPMN	SCA	SPN
Sex (% Female)	>95%	~ 55%	~70%	Females> males
Age (decade)	4th, 5th ("Mother")	6th, 7th	6th, 7th ("Grandmother")	2nd, 3rd
Asymptomatic	~ 50%	Mostly when small	~ 50%	~ 50%
Location (% body/tail)	95%	30%	50%	Predominantly
Common capsule	Yes	No	Yes	Yes
Calcification	Rare, curvilinear in the cyst wall	No	30–40%, central	Occasional
Gross appearance	Orange	Grape-like	Spongy/honeycomb like	Round, soft, encapsulated hemorrhagic mass
Multifocality	No	Yes	No	Solid and cystic components
Internal structure	Cysts in cyst	Cyst by cyst	Microcystic and/or macrocystic	Unilocular
Main PD communication	Infrequent	Yes	No	No
Overall risk of malignancy/ HGD	~10%	~7% in 10 yrs (low risk), ~24% in 10 yrs (high risk)	0.10%	~ 10%
Aspirate characteristic	Viscous	Viscous, or thin	Thin, often bloody	Bloody
Cytology Findings	Columnar cells with variable atypia, Stain mucin < 50%	Cuboidal cells +ve for glycogen (< 50%)	Columnar cells with variable atypia, Stain mucin < 50%	Branching papillae with myxoid stroma (high yield from solid component)
CEA levels	> 200 ng/ml in ~75%	< 5 – 20 ng/ml	> 200 ng/ml in ~75%	Insufficient data

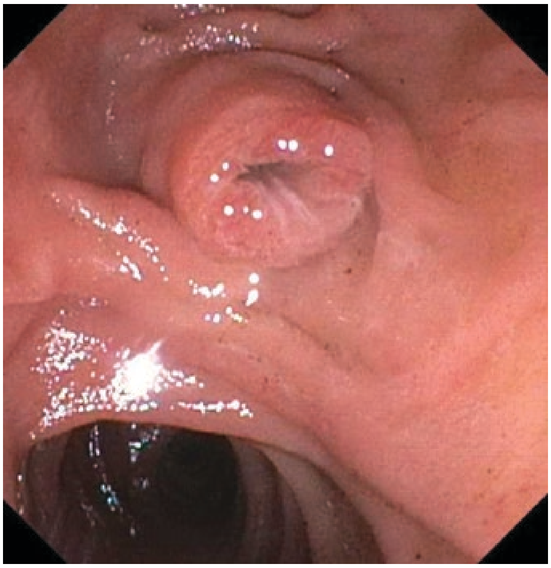

Figure 1 Main duct IPMN with a gaping papilla which is extruding mucus.

symptoms such as pancreatitis or obstructive jaundice when they enlarge, especially if located in the head of the pancreas, in which case surgical resection can be considered (Elta et al. 2018; Jais et al. 2016).

Solid Pseudopapillary Neoplasms

Solid pseudopapillary neoplasms (SPNs) are rare and are more commonly found in young women in their 20s. Radiographically, SPNs have solid growth with cystic degeneration with both solid and cystic areas noted on imaging. The age at detection is highly variable ranging from childhood to adulthood and can be found in any part of the pancreas. Even though about 10% of SPNs can be aggressive tumors they have a better prognosis than pancreatic adenocarcinoma with a 5-year disease-specific survival of 98% (Elta et al. 2018). A referral to a high-volume pancreatic center for surgical resection is recommended for all patients with SPNs.

Cystic Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pNETs) are rare tumors that usually presents in the 60s. They are non-secreting tumors and morphologically can be solid, cystic, or mixed (Elta et al. 2018). The management of these lesions is not discussed and is out of the scope of this chapter.

Non-Neoplastic and Non-Mucin Producing Pancreatic Cysts

Pseudocysts

Pseudocysts are usually found in patients with a history of pancreatitis. They are less common than PCNs but it is important to differentiate between them because pseudocysts do not have a malignant potential and thus do not require surveillance or intervention if asymptomatic. Additionally, if symptomatic, pseudocysts can be treated with endoscopic drainage alone whereas PCNs may require surgery and are not treated with endoscopic drainage. Cystic lesions in the pancreas are suspected to be a pseudocyst in patients with a prior history of pancreatitis whose cystic lesion develops on imaging after the episode of pancreatitis. In individuals with idiopathic pancreatitis over the age of 40, an underlying PCN as a cause of pancreatitis if the cystic lesion is seen on initial imaging should be strongly considered prior to labeling the cystic lesion as a pseudocyst (Elta et al. 2018).

Epidemiology of PCNs

The evolving fields of radiology and endosonography have improved the diagnostic ability to differentiate different types of PCNs but this should not overshadow the importance of several epidemiological factors that can provide useful hints toward the diagnosis. Factors such as gender, age of diagnosis, and location of the cystic lesion in the pancreas can all be used in solving the diagnostic dilemma of PCNs as detailed in Table 1.

Clinical Presentation of PCNs

Majority of PCNs are discovered incidentally in asymptomatic individuals in clinical practice but retrospective surgical case series have reported symptoms in as high as 80% of individuals with PCNs (Parra-Herran et al. 2010; Walsh et al. 2002). This high percentage is likely a result of selection and referral bias since other observational studies show the prevalence of symptoms to be much lower around ~20% (Crippa et al. 2017; Mukewar et al. 2017). Of note, symptomatic IPMNs have been noted to have an association with malignancy (OR 1.6 CI 1.0-2.6) (Anand et al. 2013). A myriad of gastrointestinal symptoms has been reported to have an association with PCNs in surgical case series [abdominal pain (69%), weight loss (38%), back pain (18%), palpable mass (5%), and postprandial fullness (4%)] but it is extremely difficult to attribute these to the PCNs due to the non-specific nature of these symptoms. On the contrary, pancreatitis (36%) and obstructive jaundice (18%) can more directly be attributable to PCNs. It is especially important to consider a PCN as the cause of pancreatitis and not misdiagnose it as a pseudocyst in patients presenting with pancreatitis above the age of 40. Furthermore, PCN related acute pancreatitis and obstructive jaundice can both be an indicator of advanced neoplasia within the PCN (or indicator that the PCN is harboring advanced neoplasia) (Del Chiaro et al. 2013; Rivera et al. 1997; Shin et al. 2010; Vege et al. 2015). Therefore, lesion related obstructive jaundice is considered an absolute criterion for surgery and lesion related acute pancreatitis is considered a “worrisome feature” and a relative indication for surgery (Tanaka et al. 2017, 2012). New-onset diabetes is also a concern in patients with IPMNs above the age of 50 since these patients are noted to have an increased risk of high-grade dysplasia or pancreatic cancer and thus a thorough evaluation is warranted with an MRI /MRCP and/or EUS (Leal et al. 2015; Mimura et al. 2010).

Diagnostic Tools for PCNs

Radiology

Cross-sectional imaging serves a dual purpose in the diagnostic evaluation of a PCN. It helps characterize the type of PCN and assesses for presence of high-grade dysplasia and/or pancreatic cancer. Different retrospective studies have shown variable rates of diagnostic accuracy of the contrast enhanced computed tomography (CECT) scans and Magnetic Resonance Imaging (MRI)/Magnetic Resonance Cholangiopancreatography (MRCP) in identifying the type of PCN as well as differentiating between benign and malignant cystic lesions. In a systematic review of 19 studies, CT can accurately pick up benign from malignant PCNs in 70–80% of the cases with a sensitivity of 80% for IPMNs. MRI/MRCP had a similar accuracy for differentiating a benign from a malignant PCN ranging from 55–76% though had a much higher sensitivity of around 96% for diagnosing IPMN (Jang et al. 2015; Jones et al. 2013; Lee et al. 2011).

MRI/MRCP is preferred over CT due to its lack of radiation and a higher sensitivity for identification of cyst communication with the pancreatic duct (that likely explains its higher accuracy for diagnosing a BD-IPMN), for detecting presence of a solid component within the cystic lesion and for identification of multifocal PCNs (Sahani et al. 2013; Waters et al. 2008). Despite its many advantages, MRI/MRCPs do have some cons including lower spatial resolution, decreased sensitivity for detecting calcification within the cystic lesion, longer imaging duration, and increased susceptibility to motion artifact. Secretin enhanced MRCP can improve the visualization of the pancreatic duct and detect communication between the pancreatic duct and the PCN when it would not be obvious otherwise though the small incremental benefit in the diagnostic yield is a questionable justification at this time for the higher cost associated with secretin use. The use of a combined approach with MRI or CT with EUS as discussed below or even Positron Emission Tomography with CT has also been suggested to increment the low diagnostic yield of single imaging modalities for differentiating benign from malignant PCNs. A small study has shown that PET combined with CT had a diagnostic yield of around 94% in this scenario as compared to 77% for CT and 86% for MRI with MRCP (Kauhanen et al. 2015).

Endoscopic retrograde cholangiopancreatography (ERCP) may have a limited role in evaluation of a MD-IPMN. The use of ERCP in routine evaluation of PCNs remains limited though due to its invasive nature and high risk of complications and cross-sectional imaging along with EUS remain the mainstay for diagnostic management of PCNs.

Radiomics

Radiomics is the analysis of mathematically derived textural features from cross-sectional imaging that are not perceptible to human eyes. Multiple studies in radiomics have employed variable extraction of radiometric data from CECTs via machine learning algorithms with some combining radiomics, cyst morphology and clinical features to differentiate types of PCNs (Dmitriev et al. 2017; Xie et al. 2020; Yang et al. 2019) and more recently, risk stratify IPMNs (Attiyeh et al. 2019; Hanania et al. 2016; Hoffman et al. 2017). While radiomics is an exciting tool in the arsenal for classification and risk stratification of PCNs, its use has largely been limited to clinical trials at large academic centers and is several years away from prime-time utilization.

Endoscopic Ultrasound

Endoscopic Ultrasound (EUS) is an extremely useful tool that aids in the diagnosis of PCNs not only as a stand along imaging technique but also via sampling of the cyst fluid and its analysis. Cyst fluid analysis increases the diagnostic yield and can especially help in the differentiation between mucin producing and non-mucin producing PCNs. EUS imaging alone (without cyst fluid analysis) is accurate in 65–96% of the cases when differentiating benign from a malignant PCN. This is similar to the accuracy of the MRI and the CT noted above and though EUS alone adds only a limited incremental value over cross-sectional imaging, it does have a higher resolution and has been demonstrated to have a higher sensitivity for identification of a mural nodule (MN) within a PCN. The mural nodule has irregular borders on EUS and usually has a hyperechoic center as opposed to a mucin ball which has a smoother wall with a hyperechoic rim and hypoechoic center (Tirkes et al. 2014). Additionally, an EUS without features of concern in a PCN has a high negative predictive value for ruling out malignancy (Scheiman et al. 2015). Despite several advantages, EUS should be used judiciously in the diagnostic management of PCNs due to its invasive nature when CT/MRI are not sufficiently diagnostic or there are cystic features of concern on cross-sectional imaging warranting further evaluation (European Study Group on Cystic Tumours of the, P. 2018; Harima et al. 2015; Tanaka et al. 2017).

Adverse events are reports in 2.7% to 5% of the cases undergoing EUS-FNA (Wang KX Assessment 2011). Most common adverse events include abdominal pain, pancreatitis and intracystic hemorrhage (Al-Haddad et al. 2008; Lee et al. 2005; Tarantino et al. 2014; Varadarajulu and Eloubeidi 2004). Cyst infection rates of as high as 14% have also been quoted in older studies (Wiersema et al. 1997) though more recent data has shown much lower rates of less than 1% (Guarner-Argente et al. 2011). The current ASGE guidelines suggest consideration of prophylactic antibiotics when performing EUS-FNA in PCNs, but this practice remains variable in the real world (Committee, A.S.o.P. et al. 2016).

Cytology, Biomarkers, and Molecular Analysis

EUS-guided fine-needle aspiration (FNA) of the pancreatic cystic fluid is considered when additional diagnostic information is warranted such as in patients being considered for surgery or in patients where a diagnosis of a serous cyst would help avoid surveillance. The cyst fluid obtained via FNA can be sent for biochemical, cytological, and molecular analysis. This can be very useful in trying to distinguish mucin producing from non-mucin producing PCNs and avoid unnecessary surveillance.

Even though **cytology** of the cyst fluid is highly specific (83–100%), it has been shown to lack sensitivity for diagnosing PCNs (27–48%) and thus has a low diagnostic accuracy (8–59%) (Stelow et al. 2003; Thosani et al. 2010; Wang et al.

2015). The lack of sensitivity is likely a result of a low number of intact exfoliated cells that are usually detected in the sample.

The analysis for fluid **CEA** and **amylase** levels is also useful when distinguishing mucinous from non-mucinous PCNs but these will not differentiate MCNs and IPMNs. A cutoff value of ≥192–200 ng/mL has previously been noted to have 79% accuracy in diagnosis of mucinous cysts (Brugge et al. 2004) but more recent studies have shown a lower sensitivity and specificity (63% and 88% respectively) that can lead to a misdiagnosis of around ~40% of mucinous cysts (Thornton et al. 2013). Additionally, higher CEA levels have not shown to correlate with risk of high-grade dysplasia and/or invasive cancer in PCNs (Brugge et al. 2004; Park et al. 2011). Cyst fluid amylase levels are mostly helpful in excluding pseudocysts when they are low but high amylase levels have limited diagnostic utility as they can be elevated in IPMNs, pseudocysts and in rare instances, MCNs as well (Ngamruengphong and Lennon 2016; Thornton et al. 2013).

Intra-cystic **glucose** levels have recently gained traction as a low-cost diagnostic test with many studies now showing that intra-cystic glucose levels are superior to CEA levels in differentiating mucinous from non-mucinous PCNs. Mucinous PCNs are expected to have low glucose levels partly due to the metabolism from the active neoplastic cells. Intra-cystic glucose concentration < 50 mg/dL has significantly better sensitivity than a CEA level > 192 ng/mL for diagnosing mucinous cysts (93.6% vs 54.8%) (Ribaldone et al. 2020). A meta-analysis of 8 studies with included 609 PCNs showed pooled sensitivities for glucose vs CEA of 91% vs 56% and pooled specificities for glucose vs CEA of 96% vs 86% (McCarty et al. 2021a).

Next-generation sequencing (NGS) allows evaluation of gene panels and whole exome in intact cell and cell-free nucleic acid present in the cyst fluid and can look for DNA mutations that are commonly associated with development of pancreatic adenocarcinoma (RAS, CDKN2A, SMAD4, PTEN, PIK3CA, and TP53). These can help with classification of mucinous versus non-mucinous PCNs as well as risk stratification of IPMNs. Presence of dual KRAS and GNAS mutations can diagnose mucinous PCNs with an accuracy of 97% (McCarty et al. 2021b). Moreover, presence of TP53, PIK3CA, and/or PTEN mutation has 88% sensitivity and 95% specificity, respectively for diagnosing IPMNs with advanced neoplasia (Singhi et al. 2018). Even though cyst fluid molecular analysis by NGS has a high accuracy in identification of the type of PCN and risk stratification for advanced neoplasia, limited availability and high cost remain big deterrents for routine use. The clinical utility of these biomarkers remains to be demonstrated.

Advanced EUS Based Techniques for Evaluation of PCNs

EUS with and without cyst analysis remains a subpar test in guiding management decisions due to low cellularity and a suboptimal diagnostic accuracy of the biomarkers. Therefore, several techniques have been developed for evaluation of cyst wall including tissue acquisition from the lining of the cyst wall for histology. Use of needle based confocal light endomicroscopy (nCLE) and through-the-needle intracystic biopsy (Moray micro forceps; US Endoscopy, Mentor, Ohio) are the techniques that have shown the most promise in increasing the diagnostic yield of EUS with an acceptable risk profile.

The **microforceps biopsy (MFB)** can be advanced through a 19G needle while performing EUS–FNA and allows for tissue sampling of the cyst wall. The technical success of the device in limited series is reported to be approximately 99% with a tissue acquisition yield of 88% and a diagnostic accuracy of 69% (Balaban et al. 2021). Adverse events are reported in around 9% of the cases and include intracystic hemorrhage, mild acute pancreatitis, abdominal pain, and post-procedural infection (Balaban et al. 2021). While EUS–FNA with MFB allows for a high diagnostic accuracy in management of PCNs, the higher risk of adverse events as compared to EUS–FNA alone is likely a deterrent for incorporation of this technique in routine clinical practice.

EUS guided nCLE is another advanced technique that allows real-time in vivo endo-microscopic imaging of the intracystic epithelium of the cyst wall. Confocal images are obtained when a low-power laser illuminates the tissue after intravenous administration of fluorescent contrast agent (such as fluorescein [CellVizio; Mauna KeaTechnologies, Paris, France]) and the reflected light is focused through a pinhole onto a detection system that transforms it to a detailed bitmap gray scale image on the computer (Neumann et al. 2010; Polglase et al. 2005). Studies have established the characteristic features of IPMNs (presence of villous structures), MCNs (a thick gray line), SCAs (a superficial vascular network pattern corresponding to a dense and subepithelial capillary vascularization only seen in SCAs), cystic neuroendocrine tumors (black neoplastic cell clusters with white fibrous areas) and pseudocysts (field of bright particles) (Napoleon et al. 2015, 2016). nCLE can differentiate mucinous PCNs and non-mucinous PCNs with a diagnostic accuracy of around 89–99%. The pooled risk of post-procedure pancreatitis is around 1% (Facciorusso et al. 2020). In addition, several imaging variables in nCLE have been identified that determine the presence of advanced neoplasia in IPMNs with papillary epithelial thickness (width ≥ 50 μm) and papillary epithelial darkness (cut-off ≤ 90 pixel intensity) having the highest interobserver agreement for detection of advanced neoplasia (Krishna et al. 2020). Similarly, a nCLE pattern of dark aggregates of neoplastic cells correlated with the morphologic features of irregular branching and budding and was diagnostic of malignancy. The cost and unproven clinical utility have limited the widespread adoption of nCLE in clinical practice.

Contrast-enhanced EUS (CE-EUS) has been proposed to be useful in the presence of MNs or solid components to assess the presence of vascularization. Even though earlier studies did not report any improvement over traditional EUS at differentiating

PCNs, more recent reports have noted an increased diagnostic yield with CE-EUS putatively because it can detect small lesions that could be missed on contrast enhanced CT or EUS-FNA (Kamata et al. 2018; Zhong et al. 2019).

Radiological Features of Concern in PCNs

There are certain radiological features that are considered to have a high risk of harboring or predicting progression to malignancy and therefore, these patients should be referred for surgery. These include presence of a vascularized or enhancing MN and MPD dilation > 1 cm as discussed later in this chapter. There are other radiological features such as MPD dilation >5 mm, cyst size ≥3 cm, rapid growth rate (>2.75 mm/year) or thick vascularized cyst walls that are also considered important but are not strong standalone predictors of malignancy and warrant further investigation and closer surveillance if surgical resection is not pursued as noted below.

Size

The size of the PCN can help guide decision-making in management of mucinous PCNs but is not a factor when it comes to management of non-mucinous PCNs. That is because SCNs do not have a higher malignancy potential regardless of their dimensions and do not need a surgical referral unless symptomatic but SPNs are referred for surgical resection even if they have a smaller diameter due to their inherent risk of malignancy. On the other hand, a larger diameter of a mucinous PCN has shown some association with an increased risk of high-grade dysplasia or invasive cancer though the data for it remains inconclusive and an optimal size cut-off for surgical resection remains debated. Various surgical case series have shown a cyst size of ≥30 mm can positively predict presence of high-grade dysplasia or invasive cancer in around ~ 30% of the case (Nguyen et al. 2015; Robles et al. 2016; Sahora et al. 2013) but other studies have not been able to reproduce these findings (Del Chiaro et al. 2017). Therefore, different guidelines have recommended a different size cut-off necessitating further evaluation. The current IAP and AGA guidelines suggest proceeding with an EUS FNA for any mucinous cystic lesion with a size ≥30 mm whereas the European guidelines use a cutoff of ≥40 mm in IPMNs and MCNs for consideration of surgery (European Study Group on Cystic Tumours of the, P. 2018). Some centers strongly consider EUS and FNA in PCNs over 2 cm in size where the diagnosis of a non-mucinous cyst may make a difference in management such as avoiding a long surveillance time period in younger patients. Using the cyst diameter in conjunction with other risk factors is considered more appropriate since it increases the sensitivity to detect malignancy as opposed to the cyst diameter alone (Ohtsuka et al. 2012).

Growth Rate

It has been reported that the PCN growth rate on surveillance is a more accurate predictor for progression rather than cyst size. Even though an increase in cyst size ≥3 mm/year or >5 mm/2 years has been noted to confer a higher risk of high-grade dysplasia or invasive cancer (5-year risk for developing malignancy is 45% for BD-IPMNs regardless of the original cyst size) (Kang et al. 2011; Kwong et al. 2015), data supporting this is limited. Additionally, high interobserver variability in the measurement of the cyst size (as high as 4 mm) has been noted which makes drawing conclusions from comparisons between surveillance cross-sectional imaging challenging to interpret (Dunn et al. 2016). Nevertheless, the IPMNs and MCNs in surveillance should be further evaluated with an EUS and FNA when cross-sectional imaging shows a rapid increase in size.

Mural Nodules (MN) or Solid Component

Mural nodules are solid expressions of tumor proliferation and presence of a MN within the PCN is one of the strongest predictors for presence of underlying high-grade dysplasia (in MD-IPMNs) or invasive cancer (in BD-IPMNs and MD-IPMNs) with an OR 9.3 (CI 5.3–16.1) (Anand et al. 2013). The presence of a MN within a PCN should warrant further evaluation with an EUS ± FNA and if a question remains about a mucin clot versus an MN, if available, CE-EUS could be considered. The dimensions of the growing MN are a result of the neoplastic burden in the PCN and risk of malignancy seems to be directly correlated to the size of MN. This is why new guidelines recommend surgical resection for all PCNs with MN ≥5 mm (European Study Group on Cystic Tumours of the, P. 2018; Kwong et al. 2015; Tanaka et al. 2017).

Dilation of Main Pancreatic Duct (MPD)

MPD dilation in IPMNs is a result of mucin produced by the neoplastic cells in the duct walls and is thought to be an indicator of an underlying high-grade lesion. All MD-IPMNs warrant surgical resection but MPD in BD-IPMNs represents somewhat of a challenge from a management perspective even though there is some consensus that the larger the duct diameter, the higher the risk of high dysplasia and invasive cancer. This is because most data that defines risk of malignancy in IPMNs is from retrospective surgical case series as noted earlier in this book chapter, that fail to accurately identify the true incidence of malignant progression in this population due to an inherent selection bias. It is reasonable to further work-up all such patients with MPD dilation to rule out other possible benign and malignant etiologies such as ductal hypertension from mucin plugging, obstructive chronic pancreatitis (pancreatic duct stricture or stones), and solid obstructive tumors especially in the head of the pancreas. Even though using MPD dilation alone to guide management decision in patients with BD-IPMNs is fraught with a risk of possible overtreatment as stated above, most authors agree that patients with an IPMN and MPD diameter of ≥10 mm should undergo surgery if they are reasonable surgical candidates. This is supported by multiple surgical series showing a rate of ~60% (range 36–100%) for high grade dysplasia and a rate of ~44% (range 11–81%) for pancreatic cancer as well as a 40% risk of IPMN related death on five-year follow up in a non-operated cohort of patients with presumed IPMNs (Crippa et al. 2017; Salvia et al. 2004; Suzuki et al. 2004). It is not as straightforward for patients with an MPD diameter between 5 and 9 mm where though some studies have suggested a high risk of malignancy of around ~ 60% (Hackert et al. 2015), others have shown a five-year disease specific survival to be > 95% (Crippa et al. 2017). Therefore, most authors suggest further evaluation with an EUS and FNA in this patient population. An abrupt change in the caliber of the MPD with upstream dilation is another concerning feature that should always warrant further investigation with an EUS and FNA as well.

Management of PCNs

Management decisions for PCNs are nuanced and it is necessary to incorporate a multitude of factors that can influence this decision-making including clinical and radiological data as well as the patient fitness for surgery. This is why it is of utmost importance that the decision should be deferred to a multidisciplinary group including gastroenterologists, radiologists, and surgeons. At baseline, all patients with a suspected PCN should get a thorough history and physical examination. Clinical variables such as patient age, family history, presence of symptoms, other medical comorbid conditions, perceived cancer risk, and patient preference for management should all be carefully evaluated. A dedicated pancreatic imaging should also be performed for all patients with a suspected PCN to evaluate for the presence of concerning features that have been described above (MRI/MRCP is preferred though a pancreatic protocol CT is a reasonable alternative). If there are any cross-sectional imaging characteristics of concern, an EUS should be performed along with FNA for cytopathology, biomarkers, and molecular testing where the expertise is available. All the information obtained should then be used to decide about the need for ongoing surveillance versus surgical resection of the PCN.

Surveillance

Surveillance is usually necessary for only PCNs that have a risk of progression to malignancy. i.e., BD-IPMNs and MCNs in patients who are surgically fit. The diagnosis of a mucinous PCN (BD-IPMN and MCN) can remain uncertain even if EUS and FNA is done since histopathology is usually not available. In such cases, surveillance is continued as one would for a mucinous PCN. Surveillance is a reasonable option for most patients with PCNs because there is strong evidence supporting low risk of progression and an indolent course in majority of these lesions especially in absence of any concerning radiographic features (Arlix et al. 2012; Lawson et al. 2015; Mukewar et al. 2017; Nagata et al. 2016). The aim of surveillance is to recognize PCNs likely to harbor high-grade dysplasia or pancreatic cancer and intervene early.

The optimal surveillance intervals remain controversial due to a paucity of high-quality data. At this time, most guidelines stratify surveillance intervals based on cyst size even though, as stated in the chapter earlier, it is a questionable marker for predicting risk of progression to malignancy in PCNs. This because it is the most practical PCN feature that can be utilized in this setting. It is important to have an experienced radiologist review high-quality imaging for all new diagnoses of PCNs to ensure there are no concerning features such as development of a mural nodule or solid component either within the cyst or the pancreatic parenchyma, MPD dilation >5 mm, cyst size ≥3 cm, rapid growth rate (> 3 mm/year or > 5 mm/2 years) or thick vascularized cyst walls. After this determination is made, two short term surveillance imaging in six months should be undertaken to ensure stability of the lesion. Further surveillance can then be carried out based on the cyst size and other features as shown in Figure 2. There are no recommendations on how long surveillance should be continued or when surveillance should be stopped.

There are other important factors to consider for surveillance of PCNs:

1 *Surveillance should be continued till the patient is no longer a surgical candidate.*

   There is no good long-term data about modification of surveillance intervals once the cyst stability has been demonstrated over five years and the benefit of prolonged follow-up in reducing cancer-related mortality has not been proven. One study has shown a low risk of progression after five years in such patients (Moris et al. 2017) and AGA guidelines even advocate for discontinuation of surveillance after five years. But most authors agree that the risk of progression is not reduced despite cyst stability at 5 years with data from genetic studies demonstrating that progression can take up between 15 and 20 years and others showing progression to invasive cancer in BD-IPMNs up to 16 years after diagnosis (Khannoussi et al. 2012; Yachida et al. 2010). Therefore, it is reasonable that patients who remain surgical candidates should continue surveillance. But it is also important to account for new comorbid conditions and determine risks of surgery as patients age so that surveillance can be discontinued when the risks of surgery can no longer be justified.

2 *There should be consistency in the use of imaging modality to avoid variability.*

   An important variable that is considered when making management decisions about PCNs is the overall cyst size

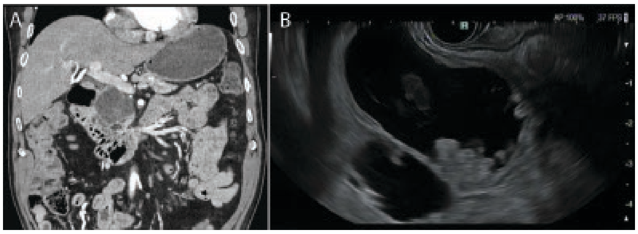

Figure 2 A) Large IPMN with a central mass B) BD-IPMN with cancer as seen on EUS.

and/or increase in cyst size on surveillance imaging. As discussed earlier, there is a significant variability in evaluation of cyst size between different imaging modalities (CT vs MRI vs EUS) (Dunn et al. 2016) and using a consistent imaging modality can help avoid this variability that can sometimes lead to unwarranted testing and procedures.

3 *Patients on surveillance with a new diagnosis of diabetes warrant evaluation and a closer surveillance.*
New-onset diabetes in patients with IPMNs, especially in those above the age of 50 have been noted to have increased risk of high-grade dysplasia or pancreatic cancer (Leal et al. 2015; Mimura et al. 2010). Therefore, a short-term surveillance in six months should be considered either with MRI/MRCP or EUS in these patients.

4 *Patients with high-risk features detected on surveillance should be referred for surgery.*
Patients who are noted to have high risk features such as MPD dilation > 1 cm, develop an enhancing MN or a solid component in the cyst or develop obstructive jaundice on surveillance should undergo resection. But shorter interval surveillance (3–6 months) can be considered in patients with the features mentioned above, who opt for increased surveillance over surgery due to operative risk or personal preference.

Surgery

Several factors play an important role when it comes to surgical decision making for patients with PCNs. As mentioned previously, there are some clinical and cyst features that have a high risk of harboring/progression to high grade dysplasia and/or invasive cancer. These include a PCN causing obstructive jaundice, presence of a vascularized or enhancing MN, MPD dilation >1 cm, and presence of cytology suggesting malignancy. If any of these features are present, surgical resection is strongly considered though it must be recognized that current guidelines and their recommendations do not have strong scientific backing with a low specificity for predicting progression to high grade dysplasia and invasive cancer. Therefore, all final surgical decisions should be individualized to each patient. Consideration for the clinical features mentioned above as well as patient-related factors such as age, life expectancy, overall health status, and motivation for surgery should be undertaken. Type of surgery is usually determined by the location of the PCN in the pancreas, and is also a major consideration in this decision-making because a pancreaticoduodenectomy for a lesion in the head of pancreas has a significantly different risk of mortality and morbidity as opposed to a distal pancreatectomy for a lesion in the tail of the pancreas.

In cases with IPMNs or MCNs suspected to have malignant progression, surgery should target complete removal of the tumor along with appropriate lymphadenectomy and negative resection margins should be ensured via intraoperative frozen sections. Parenchyma sparing pancreatectomy is not always the best approach for these patients due to the high risk of harboring malignancy and this is mostly reserved for resection of cases with symptomatic SCAs.

Follow up after Surgical Resection of a PCN

Patients with surgically resected SCA, pseudocyst or other benign cyst and MCN without an associated pancreatic cancer do not require post-operative surveillance but all patients with IPMN including the ones with negative surgical margins should undergo long-term surveillance after surgery as there is a considerable risk of development of a new IPMN that will require surgery and/or concomitant pancreatic ductal adenocarcinoma which can develop even more than 10 years after the initial operation (Ikeuchi et al. 2010; Sahora et al. 2016). The recurrence rates for IPMNs are reported in around 1–20% of the case whereas the risk of malignancy is around 2–7.8% (Chari et al. 2002; Miller et al. 2011; Salvia et al. 2009; White et al. 2007). The recommended follow up interval is shorter (6 months) for high-risk patients such as those with family history of pancreatic cancer and a positive surgical margin while it is longer (12 months) for other patients (Tanaka et al. 2017). This is thought to be a result of the "field defect" mentioned earlier in the chapter present in the entire pancreatic parenchyma that predisposes the remnant to development of new IPMNs, progression of any remaining IPMNs or development of concomitant pancreatic cancer.

Endoscopic Ablation

The variable clinical behavior and morbidity of surgical approach for PCNs makes it necessary to venture into minimally invasive options for treatment of PCNs. Along these lines, endoscopic ultrasound guided ablation of the PCNs has been investigated using ethanol alone or ethanol followed by the instillation of the chemotherapy agent paclitaxel. Paclitaxel works by stabilizing microtubules thus inhibiting cell replication and is hydrophobic which improves retention in the cyst by decreasing peri-cystic leakage. The results have been mixed with varying degrees of success including imaging guided cyst resolution rates of around 33–79% of the cases and varying degrees of epithelial ablation on histopathology of resected specimens (DeWitt et al. 2009; DiMaio et al. 2011; Gan et al. 2005; Gomez et al. 2016; Moyer et al. 2016). The technique is in infancy stages with multiple issues that still need to be sorted out including concerns with incomplete epithelial infiltration from the ethanol as well as need for ongoing surveillance imaging once the cyst has collapsed which is challenging. Additionally, there are no data supporting eradication of the risk of malignant progression with decreasing cyst size and development of pancreatic ductal adenocarcinoma (PDAC) at the site of a previously treated BD-IPMN after 41 months of follow up has been reported (Gomez et al. 2016). Complication rates are reported in around ~12% of the cases and include fever, abdominal pain, pancreatitis, peritonitis, and splenic vein obliteration (DeWitt et al. 2014; Gan et al. 2005; Oh et al. 2008). Due to the reasons mentioned above, routine use of EUS guided ablation of the PCNs is currently not recommended and should only be considered at large volume centers in patients who refuse surgery or are high risk surgical candidates. This should ideally be done in a clinical trial setting to obtain more data on appropriate technique and materials as well as on the long-term outcomes of this procedure.

EUS guided radiofrequency ablation (RFA) has also been evaluated in a few human case series but has mostly been limited to patients with pancreatic cancer and pancreatic neuroendocrine tumors. A small study has evaluated EUS guided RFA for PCNs in six patients (4 with mucinous cysts, one with BD-IPMN and 1 microcystic adenoma) and demonstrated image guided resolution in two cases and a ~50% decrease in size in three of the cases (Pai et al. 2015). Reported adverse outcomes were self-limiting abdominal pain in two patients. While these results are promising, more research on this technique is needed before a verdict can be reached on its efficacy.

Comparison of Different Society Guidelines for Management of Pancreatic Cystic Neoplasms

Different organizations have published guidelines on management strategies for patients with PCNs. Even though there are remarkable similarities between most of these guidelines, which is reassuring, there are some notable differences which is why the authors of this chapter felt that including a summary about these is necessary. Most guidelines focus on management of incidentally discovered pancreatic cystic lesions such as ACG, AGA, ASGE, European guidelines, and American college of radiology guidelines. The revised Fukuoka guidelines, which are the most comprehensive in the authors' opinions, only focus on IPMNs. Major differences include when to recommend for evaluation with EUS-FNA and surgical resection . Studies have also attempted to compare these guidelines in their ability to recognize high risk PCNs using surgically resected specimens as the gold standard. The respective accuracy, sensitivities, and specificities of the guidelines are: AGA guidelines 2015 – 49.6%, 23.5% and 84.3%, Revised Fukuoka guidelines 2017 – 41.2%, 39.7% and 43.1%, and European guidelines 2018 – 58%, 67.7% and 45.1% respectively (Ardeshna et al. 2022). The suggested algorithm currently used at the author's institution for management of PCNs is displayed in Figure 3 below.

Conclusion

Pancreatic cystic neoplasms have increased in incidence over the years and represent a major diagnostic and management dilemma for gastroenterologists, resulting in significant uncertainty and anxiety to patients and providers. A large majority of these PCNs are BD-IPMNs and the current evidence for management is severely lacking in high quality research. Regardless, it is imperative that all management decisions should be tailored to individual patients based on their specific clinical factors, radiographic features of their PCN, and their surgical candidacy. More prospective multicenter studies evaluating different management approaches as well as innovation in the currently available techniques for the accurate diagnosis of PCNs are much needed to help streamline decision making in this challenging field.

Key Take Home Messages

- Only mucin producing PCNs (MCNs and IPMNs) have a clinically relevant risk of malignant transformation
- Most controversy surrounds management of BD-IPMNs since differentiation from other types of PCNs is challenging and there is paucity of high-quality data for optimal management.
- Identification of SPNs, MD-IPMNs, pNETs and larger MCNs is less challenging and the accepted approach is surgical resection if the patient is a suitable candidate

Areas for Further Research

Improved non-invasive surveillance methods for medium risk lesions

Chemopreventive regimens for low risk lesions

Trusted Websites for Further Reading

https://www.pancreaticcancer.org.uk/information/just-diagnosed-with-pancreatic-cancer/pancreatic-cysts

https://www.mayoclinic.org/diseases-conditions/pancreatic-cysts/diagnosis-treatment/drc-20375997

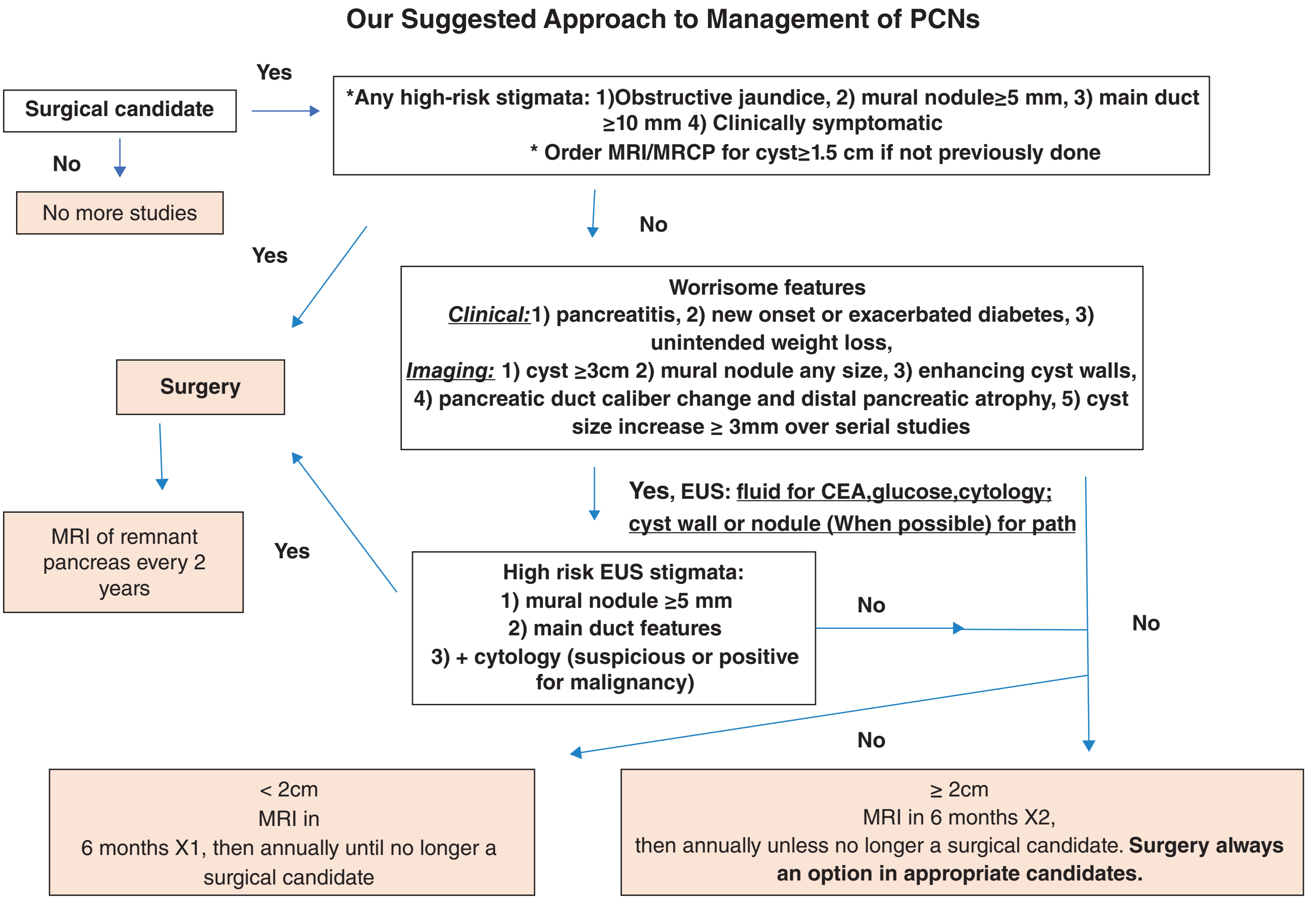
Our Suggested Approach to Management of PCNs
Surgical candidate
Yes
*Any high-risk stigmata: 1)Obstructive jaundice, 2) mural nodule≥5 mm, 3) main duct ≥10 mm 4) Clinically symptomatic
* Order MRI/MRCP for cyst≥1.5 cm if not previously done
No
No more studies
No
Yes
Worrisome features
Clinical:1) pancreatitis, 2) new onset or exacerbated diabetes, 3) unintended weight loss,
Imaging: 1) cyst ≥3cm 2) mural nodule any size, 3) enhancing cyst walls, 4) pancreatic duct caliber change and distal pancreatic atrophy, 5) cyst size increase ≥ 3mm over serial studies
Surgery
Yes, EUS: fluid for CEA,glucose,cytology; cyst wall or nodule (When possible) for path
MRI of remnant pancreas every 2 years
Yes
High risk EUS stigmata:
1) mural nodule ≥5 mm
2) main duct features
3) + cytology (suspicious or positive for malignancy)
No
No
No
< 2cm
MRI in
6 months X1, then annually until no longer a surgical candidate
≥ 2cm
MRI in 6 months X2,
then annually unless no longer a surgical candidate. Surgery always an option in appropriate candidates.

Figure 3 Suggested Algorithm for management of pancreatic cystic lesions (Adapted from Tanaka et al., 2017).

Conflict of Interest Statements

Umar Hayat MD: The author has no significant conflicts of interest with any companies or organization whose products or services may be discussed in this article.

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References

Al-Haddad, M., Wallace, M.B., Woodward, T.A. et al. (2008). The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. *Endoscopy* 40 (3): 204–208. doi: 10.1055/s-2007-995336.

Anand, N., Sampath, K., and Wu, B.U. (2013). Cyst features and risk of malignancy in intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. *Clin Gastroenterol Hepatol* 11 (8): 913–921 quiz e59-60. doi: 10.1016/j.cgh.2013.02.010.

Ardeshna, D.R., Cao, T., Rodgers, B. et al. (2022). Recent advances in the diagnostic evaluation of pancreatic cystic lesions. *World J Gastroenterol* 28 (6): 624–634. doi: 10.3748/wjg.v28.i6.624.

Arlix, A., Bournet, B, Otal, P. et al. (2012). Long-term clinical and imaging follow-up of nonoperated branch duct form of intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 41 (2): 295–301. doi: 10.1097/MPA.0b013e3182285cc8.

Attiyeh, M.A., Chakraborty, J., Gazit, L.et al. (2019). Preoperative risk prediction for intraductal papillary mucinous neoplasms by quantitative CT image analysis. *HPB (Oxford)* 21 (2): 212–218. doi: 10.1016/j.hpb.2018.07.016.

Balaban, V.D., Cazacu, I.M., Pinte, L. et al. (2021). EUS-through-the-needle microbiopsy forceps in pancreatic cystic lesions: a systematic review. *Endosc Ultrasound* 10 (1): 19–24. doi: 10.4103/eus.eus_23_20.

Brugge, W.R., Lewandrowski, K., Lee-Lewandrowski, E. et al. (2004). Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 126 (5): 1330–1336. doi: 10.1053/j.gastro.2004.02.013.

Chang, Y.R., Park, J.K., Jang, J.Y. et al. (2016). Incidental pancreatic cystic neoplasms in an asymptomatic healthy population of 21,745 individuals: Large-scale, single-center cohort study. *Medicine (Baltimore)* 95 (51): e5535. doi: 10.1097/MD.0000000000005535.

Chari, S.T., Yadav, D., Smyrk, T.C. et al. (2002). Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterology* 123 (5): 1500–1507. doi: 10.1053/gast.2002.36552.

Committee, A.S.o.P., Muthusamy, V.R., Chandrasekhara, V., et al. (2016). The role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms. *Gastrointest Endosc* 84 (1): 1–9. doi: 10.1016/j.gie.2016.04.014.

Crippa, S., Bassi, C., Salvia, R. et al. (2017). Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis. *Gut* 66 (3): 495–506. doi: 10.1136/gutjnl-2015-310162.

de Jong, K., Nio, C.Y., Hermans, J.J. et al. (2010). High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol* 8 (9): 806–811. doi: 10.1016/j.cgh.2010.05.017.

Del Chiaro, M., Verbeke, C., Salvia, R. et al. (2013). European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis* 45 (9): 703–711. doi: 10.1016/j.dld.2013.01.010.

Del Chiaro, M., Ateeb, Z, Hansson, M.R. et al. (2017). Survival analysis and risk for progression of intraductal papillary mucinous neoplasia of the pancreas (IPMN) under surveillance: a single-institution experience. *Ann Surg Oncol* 24 (4): 1120–1126. doi: 10.1245/s10434-016-5661-x.

DeWitt, J., McGreevy, K., Schmidt, C.M., Brugge, W.R.. et al. (2009). EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc* 70 (4): 710–723. doi: 10.1016/j.gie.2009.03.1173.

DeWitt, J.M., Al-Haddad, M., Sherman, S. et al. (2014). Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. *Endoscopy* 46 (6): 457–464. doi: 10.1055/s-0034-1365496.

DiMaio, C.J., DeWitt, J.M., and Brugge, W.R. (2011). Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. *Pancreas* 40 (5): 664–668. doi: 10.1097/MPA.0b013e3182128d06.

Dmitriev, K., Kaufman, A.E., Javed, A.A. et al. (2017). Classification of pancreatic cysts in computed tomography images using a random forest and convolutional neural network ensemble. *Med Image Comput Assist Interv* 10435: 150–158. doi: 10.1007/978-3-319-66179-7_18.

Dunn, D.P., Brook, O.R., Brook, A. et al. (2016). Measurement of pancreatic cystic lesions on magnetic resonance imaging: efficacy of standards in reducing inter-observer variability. *Abdom Radiol (NY)* 41 (3): 500–507.

Elta, G.H., Enestvedt, B.K., Sauer,B.G., Lennon, A.M. (2018). ACG clinical guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol* 113 (4): 464–479. doi: 10.1038/ajg.2018.14.

European Study Group on Cystic Tumours of the, P. (2018). European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 67 (5): 789–804. doi: 10.1136/gutjnl-2018-316027.

Facciorusso, A., Buccino, V.R., and Sacco, R. (2020). Needle-based confocal laser endomicroscopy in pancreatic cysts: a meta-analysis. *Eur J Gastroenterol Hepatol* 32 (9): 1084–1090. doi: 10.1097/MEG.0000000000001728.

Falqueto, A., Pelandre, G.L., da Costa, M.Z.G., Nacif, M.S., and Marchiori, E. (2018). Prevalence of pancreatic cystic neoplasms on imaging exams: association with signs of malignancy risk. *Radiol Bras* 51 (4): 218–224. doi: 10.1590/0100-3984.2017.0105.

Gan, S.I., Thompson, C.C., Lauwers, G.Y. et al. (2005). Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc* 61 (6): 746–752. doi:10.1016/s0016-5107(05)00320-2.

Gardner T.B., Glass L.M., Smith K.D. et al. (2013). Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. *Am J Gastroenterol* 108 (10): 1546–1550. doi: 10.1038/ajg.2013.103.

Girometti, R., Intini, S., Brondani, G. et al. (2011). Incidental pancreatic cysts on 3D turbo spin echo magnetic resonance cholangiopancreatography: prevalence and relation with clinical and imaging features. *Abdom Imaging* 36 (2): 196–205. doi: 10.1007/s00261-010-9618-4.

Goh, B.K., Tan, Y.M., Chung, Y.F. et al. (2006). A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma: clinicopathological features of 344 patients. *World J Surg* 30 (12): 2236–2245. doi: 10.1007/s00268-006-0126-1.

Goh, B.K., Thng, C.H., Tan, D.M. et al. (2014). Evaluation of the Sendai and 2012 international consensus guidelines based on cross-sectional imaging findings performed for the initial triage of mucinous cystic lesions of the pancreas: a single institution experience with 114 surgically treated patients. *Am J Surg* 208 (2): 202–209. doi:10.1016/j.amjsurg.2013.09.031.

Gomez, V., Takahashi, N., Levy, M.J., et al. (2016). EUS-guided ethanol lavage does not reliably ablate pancreatic cystic neoplasms (with video). *Gastrointest Endosc* 83 (5): 914–920. doi:10.1016/j.gie.2015.08.069.

Guarner-Argente, C., Shah, P., Buchner, A. et al. (2011). Use of antimicrobials for EUS-guided FNA of pancreatic cysts: a retrospective, comparative analysis. *Gastrointest Endosc* 74 (1): 81–86. doi:10.1016/j.gie.2011.03.1244.

Hackert, T., Fritz, S., Klauss, M., et al. (2015). Main-duct intraductal papillary mucinous neoplasm: high cancer risk in duct diameter of 5 to 9 mm. *Ann Surg* 262 (5): 875–880; doi: 10.1097/SLA.0000000000001462. discussion 880-1.

Hanania, A.N., Bantis, L.E., Feng, Z. et al. (2016). Quantitative imaging to evaluate malignant potential of IPMNs. *Oncotarget* 7 (52): 85776–85784. doi: 10.18632/oncotarget.11769.

Harima, H., Kaino S., Shinoda, S. et al. (2015). Differential diagnosis of benign and malignant branch duct intraductal papillary mucinous neoplasm using contrast-enhanced endoscopic ultrasonography. *World J Gastroenterol* 21 (20): 6252–6260. doi: 10.3748/wjg.v21.i20.6252.

Hoffman, D.H., Ream, J.M., Hajdu, C.H. et al. (2017). Utility of whole-lesion ADC histogram metrics for assessing the malignant potential of pancreatic intraductal papillary mucinous neoplasms (IPMNs). *Abdom Radiol (NY)* 42 (4): 1222–1228. doi: 10.1007/s00261-016-1001-7.

Ikeuchi, N., Itoi, T., Sofuni, A. et al. (2010). Prognosis of cancer with branch duct type IPMN of the pancreas. *World J Gastroenterol* 16 (15): 1890–1895. doi: 10.3748/wjg.v16.i15.1890.

Jais, B., Rebours, V., Malleo, G. et al. (2016). Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). *Gut* 65 (2): 305–312. doi: 10.1136/gutjnl-2015-309638.

Jang, D.K., Song, B.J., Ryu, J.K. et al. (2015). Preoperative diagnosis of pancreatic cystic lesions: the accuracy of endoscopic ultrasound and cross-sectional imaging. *Pancreas* 44 (8): 1329–1333. doi:10.1097/MPA.0000000000000396.

Jones, M.J., Buchanan, A.S., Neal, C.P. et al. (2013). Imaging of indeterminate pancreatic cystic lesions: a systematic review. *Pancreatology* 13 (4): 436–442. doi: 10.1016/j.pan.2013.05.007.

Kamata, K., Takenaka, M., Minaga, K. et al. (2018). Value of additional endoscopic ultrasonography for surveillance after surgical removal of intraductal papillary mucinous neoplasms. *Dig Endosc* 30 (5): 659–666. doi: 10.1111/den.13176.

Kang, M.J., Jang, J.Y., Kim, S.J.. et al. (2011). Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. *Clin Gastroenterol Hepatol* 9 (1): 87–93. doi:10.1016/j.cgh.2010.09.008.

Kauhanen, S., Rinta-Kiikka, I., Kemppainen, J. et al. (2015). Accuracy of 18F-FDG PET/CT, multidetector CT, and MR imaging in the diagnosis of pancreatic cysts: a prospective single-center study. *J Nucl Med* 56 (8): 1163–1168. doi: 10.2967/jnumed.114.148940.

Khannoussi, W., Vullierme, M.P., Rebours, V. et al. (2012). The long term risk of malignancy in patients with branch duct intraductal papillary mucinous neoplasms of the pancreas. *Pancreatology* 12 (3): 198–202. doi:10.1016/j.pan.2012.03.056.

Kitagawa, Y., Unger, T.A., Taylor, S., Kozarek, R.A., and Traverso, L.W. (2003). Mucus is a predictor of better prognosis and survival in patients with intraductal papillary mucinous tumor of the pancreas. *J Gastrointest Surg* 7 (1): 12–19. doi: 10.1016/S1091-255X(02)00152-X.

Klibansky, D.A., Reid-Lombardo, K.M., Gordon, S.R., and Gardner, T.B. (2012). The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. *Clin Gastroenterol Hepatol* 10 (5): 555–558. doi: 10.1016/j.cgh.2011.12.029.

Krishna, S.G., Hart, PA., and DeWitt, J.M. (2020). EUS-guided confocal laser endomicroscopy: prediction of dysplasia in intraductal papillary mucinous neoplasms (with video). *Gastrointest Endosc* 91 (3): 551–563; e5. doi: 10.1016/j.gie.2019.09.014.

Kromrey, M.L., Bulow, R, Hubner, J. et al. (2018). Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut* 67 (1): 138–145. doi: 10.1136/gutjnl-2016-313127.

Kwong, W.T., Lawson, R.D., Hunt, G. et al. (2015). Rapid growth rates of suspected pancreatic cyst branch duct intraductal papillary mucinous neoplasms predict malignancy. *Dig Dis Sci* 60 (9): 2800–2806. doi: 10.1007/s10620-015-3679-8.

Lafemina, J., Katabi, N., Klimstra, D., et al. (2013). Malignant progression in IPMN: a cohort analysis of patients initially selected for resection or observation. *Ann Surg Oncol* 20 (2): 440–447. doi: 10.1245/s10434-012-2702-y.

Laffan, T.A., Horton, K.M., Klein, A.P. et al. (2008). Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 191 (3): 802–807. doi: 10.2214/AJR.07.3340.

Lawson, R.D., Hunt, G.C., Giap, A.Q. et al. (2015). Pancreatic cysts suspected to be branch duct intraductal papillary mucinous neoplasm without concerning features have low risk for development of pancreatic cancer. *Ann Gastroenterol* 28 (4): 487–494.

Leal, J.N., Kingham, T.P., D'Angelica, M.I. et al. (2015). Intraductal papillary mucinous neoplasms and the risk of diabetes mellitus in patients undergoing resection versus observation. *J Gastrointest Surg* 19 (11): 1974–1981. doi: 10.1007/s11605-015-2885-1.

Lee, H.J., Kim M.J., Choi, J.Y., Hong, H.S., Kim, K.A. (2011). Relative accuracy of CT and MRI in the differentiation of benign from malignant pancreatic cystic lesions. *Clin Radiol* 66 (4): 315–321. doi: 10.1016/j.crad.2010.06.019.

Lee, L.S., Saltzman J.R., Bounds, B.C. et al. (2005). EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. *Clin Gastroenterol Hepatol* 3 (3): 231–236. doi: 10.1016/s1542-3565(04)00618-4.

Maguchi, H., Tanno, S., Mizuno, N. et al. (2011). Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. *Pancreas* 40 (3): 364–370. doi: 10.1097/MPA.0b013e31820a5975.

Maire, F., Couvelard, A., Hammel, P. et al. (2003). Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. *Gastrointest Endosc* 58 (5): 701–706. doi: 10.1016/s0016-5107(03)02032-7.

Malleo, G., Marchegiani, G., Borin, A. et al. (2015). Observational study of the incidence of pancreatic and extrapancreatic malignancies during surveillance of patients with branch-duct intraductal papillary mucinous neoplasm. *Ann Surg* 261 (5): 984–990. doi: 10.1097/SLA.0000000000000884.

McCarty, T.R., Garg, R., and Rustagi, T. (2021a). Pancreatic cyst fluid glucose in differentiating mucinous from nonmucinous pancreatic cysts: a systematic review and meta-analysis. *Gastrointest Endosc* 94 (4): 698–712 e6. doi:10.1016/j.gie.2021.04.025.

McCarty, T.R., Paleti, S., and Rustagi, T. (2021b). Molecular analysis of EUS-acquired pancreatic cyst fluid for KRAS and GNAS mutations for diagnosis of intraductal papillary mucinous neoplasia and mucinous cystic lesions: a systematic review and meta-analysis. *Gastrointest Endosc* 93 (5): 1019–1033 e5. doi: 10.1016/j.gie.2020.12.014.

Miller, J.R., Meyer, J.E., Waters, J.A. et al. (2011). Outcome of the pancreatic remnant following segmental pancreatectomy for non-invasive intraductal papillary mucinous neoplasm. *HPB (Oxford)* 13 (11): 759–766. doi: 10.1111/j.1477-2574.2011.00354.x.

Mimura, T., Masuda, A., Matsumoto, I.. et al. (2010). Predictors of malignant intraductal papillary mucinous neoplasm of the pancreas. *J Clin Gastroenterol* 44 (9): e224–9. doi: 10.1097/MCG.0b013e3181d8fb91.

Moris, M., Raimondo, M., Woodward, T.A. et al. (2017). International intraductal papillary mucinous neoplasms registry: long-term results based on the new guidelines. *Pancreas* 46 (3): 306–310. doi: 10.1097/MPA.0000000000000750.

Moyer, M.T., Dye, C.E., Sharzehi, S.. et al. (2016). Is alcohol required for effective pancreatic cyst ablation? The prospective randomized CHARM trial pilot study. *Endosc Int Open* 4 (5): E603–7. doi: 10.1055/s-0042-105431.

Mukewar, S., de Pretis, N., Aryal-Khanal, A. et al. (2017). Fukuoka criteria accurately predict risk for adverse outcomes during follow-up of pancreatic cysts presumed to be intraductal papillary mucinous neoplasms. *Gut* 66 (10): 1811–1817.doi: 10.1136/gutjnl-2016-311615.

Nagata, N., Kawazoe, A., Mishima, S.. et al. (2016). Development of pancreatic cancer, disease-specific mortality, and all-cause mortality in patients with nonresected IPMNs: a long-term cohort study. *Radiology* 278 (1): 125–134. doi: 10.1148/radiol.2015150131.

Napoleon, B., Lemaistre, A.I., Pujol, B. et al. (2015). A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy. *Endoscopy* 47 (1): 26–32. doi: 10.1055/s-0034-1390693.

Napoleon, B., Lemaistre, A.I., Pujol, B. et al. (2016). In vivo characterization of pancreatic cystic lesions by needle-based confocal laser endomicroscopy (nCLE): proposition of a comprehensive nCLE classification confirmed by an external retrospective evaluation. *Surg Endosc* 30 (6): 2603–2612. doi: 10.1007/s00464-015-4510-5.

Neumann, H., Vieth, M., Raithel, M. et al. (2010). Confocal laser endomicroscopy for the in vivo detection of intraepithelial neoplasia in Peutz-Jeghers polyps. *Endoscopy* 42 (Suppl 2): E139–40. doi: 10.1055/s-0029-1244052.

Ngamruengphong, S. and Lennon, A.M. (2016). Analysis of pancreatic cyst fluid. *Surg Pathol Clin* 9 (4): 677–684. doi: 10.1016/j.path.2016.05.010.

Nguyen, A.H., Toste, P.A., Farrell, J.J. et al. (2015). Current recommendations for surveillance and surgery of intraductal papillary mucinous neoplasms may overlook some patients with cancer. *J Gastrointest Surg* 19 (2): 258–265. doi: 10.1007/s11605-014-2693-z.

Oh, H.C., Seo, D.W., Lee, T.Y. et al. (2008). New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 67 (4): 636–642. doi:10.1016/j.gie.2007.09.038.

Ohtsuka, T., Kono, H., Nagayoshi, Y. et al. (2012). An increase in the number of predictive factors augments the likelihood of malignancy in branch duct intraductal papillary mucinous neoplasm of the pancreas. *Surgery* 151 (1): 76–83. doi: 10.1016/j.surg.2011.07.009.

Pai, M., Habib, N., Senturk, H. et al. (2015). Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. *World J Gastrointest Surg* 7 (4): 52–59. doi: 10.4240/wjgs.v7.i4.52.

Park, J.W., Jang, J.Y., Kang, M.J. et al. (2014). Mucinous cystic neoplasm of the pancreas: is surgical resection recommended for all surgically fit patients? *Pancreatology* 14 (2): 131–136. doi: 10.1016/j.pan.2013.12.006.

Park, W.G., Mascarenhas, R., Palaez-Luna, M. et al. (2011). Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. *Pancreas* 40 (1): 42–45. doi: 10.1097/MPA.0b013e3181f69f36.

Parra-Herran, C.E., Garcia, M.T., Herrera, L., Bejarano P.A. (2010). Cystic lesions of the pancreas: clinical and pathologic review of cases in a five year period. *JOP* 11 (4): 358–364.

Polglase, A.L., McLaren, W.J., Skinner, S.A. et al. (2005). A fluorescence confocal endomicroscope for in vivo microscopy of the upper- and the lower-GI tract. *Gastrointest Endosc* 62 (5): 686–695. doi: 10.1016/j.gie.2005.05.021.

Ribaldone, D.G., Bruno, M., Gaia, S. et al. (2020). Differential diagnosis of pancreatic cysts: a prospective study on the role of intra-cystic glucose concentration. *Dig Liver Dis* 52 (9): 1026–1032. doi: 10.1016/j.dld.2020.06.038.

Rivera, J.A., Fernandez-del Castillo, C., Pins M. et al. (1997). Pancreatic mucinous ductal ectasia and intraductal papillary neoplasms. A single malignant clinicopathologic entity. *Ann Surg* 225 (6): 637–644; doi: 10.1097/00000658-199706000-00001. discussion 644-6.

Robles, E.P., Maire, F., Cros, J. et al. (2016). Accuracy of 2012 International Consensus Guidelines for the prediction of malignancy of branch-duct intraductal papillary mucinous neoplasms of the pancreas. *United European Gastroenterol J* 4 (4): 580–586. doi: 10.1177/2050640615623370.

Rodriguez, J.R., Salvia, R., Crippa, S. et al. (2007). Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. *Gastroenterology* 133 (1): 72–79. doi: 10.1053/j.gastro.2007.05.010. quiz 309-10.

Sahani, D.V., Kambadakone, A., Macari, M. et al. (2013). Diagnosis and management of cystic pancreatic lesions. *AJR Am J Roentgenol* 200 (2): 343–354. doi: 10.2214/AJR.12.8862.

Sahora, K., Mino-Kenudson, M., Brugge, W. et al. (2013). Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. *Ann Surg* 258 (3): 466–475. doi: 10.1097/SLA.0b013e3182a18f48.

Sahora, K., Crippa, S., Zamboni, G. et al. (2016). Intraductal papillary mucinous neoplasms of the pancreas with concurrent pancreatic and periampullary neoplasms. *Eur J Surg Oncol* 42 (2): 197–204. doi: 10.1016/j.ejso.2015.10.014.

Salvia, R., Fernandez-del Castillo, C., Bassi, C. et al. (2004). Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg* 239 (5): 678–685. doi: 10.1097/01.sla.0000124386.54496.15. discussion 685-7.

Salvia, R., Partelli, S., Crippa, S. et al. (2009). Intraductal papillary mucinous neoplasms of the pancreas with multifocal involvement of branch ducts. *Am J Surg* 198 (5): 709–714. doi: 10.1016/j.amjsurg.2008.10.022.

Scheiman, J.M., Hwang, J.H., and Moayyedi, P. (2015). American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 148 (4): 824–848 e22. doi: 10.1053/j.gastro.2015.01.014.

Shin, S.H., Han, D.J., Park, K.T. et al. (2010). Validating a simple scoring system to predict malignancy and invasiveness of intraductal papillary mucinous neoplasms of the pancreas. *World J Surg* 34 (4): 776–783. doi: 10.1007/s00268-010-0416-5.

Singhi, A.D., McGrath, K., Brand, R.E. et al. (2018). Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut* 67 (12): 2131–2141. doi: 10.1136/gutjnl-2016-313586.

Stelow, E.B., Stanley, M.W., Bardales, R.H. et al. (2003). Intraductal papillary-mucinous neoplasm of the pancreas. The findings and limitations of cytologic samples obtained by endoscopic ultrasound-guided fine-needle aspiration. *Am J Clin Pathol* 120 (3): 398–404. doi: 10.1309/CEPK-542W-3885-2LP8.

Suzuki, Y., Atomi, Y., Sugiyama, M. et al. (2004). Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. *Pancreas* 28 (3): 241–246. doi: 10.1097/00006676-200404000-00005.

Tanaka, M., Fernandez-del Castillo, C., Adsay, V. et al. (2012). International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 12 (3): 183–197. doi: 10.1016/j.pan.2012.04.004.

Tanaka, M., Fernandez-Del Castillo, C., Kamisawa, T. et al. (2017). Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology* 17 (5): 738–753. doi: 10.1016/j.pan.2017.07.007.

Tanno, S., Nakano, Y., Koizumi, K.. et al. (2010). Pancreatic ductal adenocarcinomas in long-term follow-up patients with branch duct intraductal papillary mucinous neoplasms. *Pancreas* 39 (1): 36–40. doi: 10.1097/MPA.0b013e3181b91cd0.

Tarantino, I., Fabbri, C., Di Mitri, R. et al. (2014). Complications of endoscopic ultrasound fine needle aspiration on pancreatic cystic lesions: final results from a large prospective multicenter study. *Dig Liver Dis* 46 (1): 41–44. doi: 10.1016/j.dld.2013.08.134.

Thornton, G.D., McPhail, M.J., Nayagam, S. et al. (2013). Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: a meta-analysis. *Pancreatology* 13 (1): 48–57. doi: 10.1016/j.pan.2012.11.313.

Thosani, N., Thosani, S., Qiao, W. et al. (2010). Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. *Dig Dis Sci* 55 (10): 2756–2766. doi: 10.1007/s10620-010-1361-8.

Tirkes, T., Aisen, A.M., Cramer, H.M. et al. (2014). Cystic neoplasms of the pancreas; findings on magnetic resonance imaging with pathological, surgical, and clinical correlation. *Abdom Imaging* 39 (5): 1088–1101. doi: 10.1007/s00261-014-0138-5.

Varadarajulu, S. and Eloubeidi, M.A. (2004). Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc* 60 (4): 631–635. doi: 10.1016/s0016-5107(04)01891-7.

Vege, S.S., Ziring, B., Jain, R. et al. (2015). American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 148 (4): 819–822. doi: 10.1053/j.gastro.2015.01.015. quize12-3.

Walsh, R.M., Henderson, J.M., Vogt, D.P. et al. (2002). Prospective preoperative determination of mucinous pancreatic cystic neoplasms. *Surgery* 132 (4): 628–633. doi: 10.1067/msy.2002.127543. discussion 633-4.

Wang, Q.X., Xiao, J., Orange, M. et al. (2015). EUS-Guided FNA for Diagnosis of Pancreatic Cystic Lesions: a Meta-Analysis. *Cell Physiol Biochem* 36 (3): 1197–1209. doi: 10.1159/000430290.

Waters, J.A., Schmidt, C.M., Pinchot, J.W. et al. (2008). CT vs MRCP: optimal classification of IPMN type and extent. *J Gastrointest Surg* 12 (1): 101–109. doi: 10.1007/s11605-007-0367-9.

White, R., D'Angelica, M., Katabi, N. et al. (2007). Fate of the remnant pancreas after resection of noninvasive intraductal papillary mucinous neoplasm. *J Am Coll Surg* 204 (5): 987–993. doi: 10.1016/j.jamcollsurg.2006.12.040. discussion 993-5.

Wiersema, M.J., Vilmann, P., Giovannini, M., Chang, K.J., Wiersema, L.M. et al. (1997). Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 112 (4): 1087–1095. doi: 10.1016/s0016-5085(97)70164-1.

Xie, H., Ma, S., Guo, X., Zhang, X., and Wang, X. (2020). Preoperative differentiation of pancreatic mucinous cystic neoplasm from macrocystic serous cystic adenoma using radiomics: preliminary findings and comparison with radiological model. *Eur J Radiol* 122: 108747. doi:10.1016/j.ejrad.2019.108747.

Yachida, S., Jones, S., Bozic, I. et al. (2010). Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 467 (7319): 1114–1117. doi: 10.1038/nature09515.

Yang, J., Guo, X., Zhang, H. et al. (2019). Differential diagnosis of pancreatic serous cystadenoma and mucinous cystadenoma: utility of textural features in combination with morphological characteristics. *BMC Cancer* 19 (1): 1223. doi: 10.1186/s12885-019-6421-7.

Yoon, J.G., Smith, D., Ojili, V. et al. (2021). Pancreatic cystic neoplasms: a review of current recommendations for surveillance and management. *Abdom Radiol (NY)* 46 (8): 3946–3962. doi: 10.1007/s00261-021-03030-x.

Zerboni, G., Signoretti, M., Crippa, S. et al. (2019). Systematic review and meta-analysis: prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals. *Pancreatology* 19 (1): 2–9. doi: 10.1016/j.pan.2018.11.014.

Zhong, L., Chai, N., Linghu, E. et al. (2019). A prospective study on contrast-enhanced endoscopic ultrasound for differential diagnosis of pancreatic cystic neoplasms. *Dig Dis Sci* 64 (12): 3616–3622. doi: 10.1007/s10620-019-05718-z.

Section IV Specialist Abdominal Cancer Management Teams

23 Epidemiology, Pathology, Diagnosis, Prevention, and Management of GI Stromal Tumors and Other GI Sarcomas

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[Aspects of disease affecting the small bowel are covered in Chapter 8].

Gastrointestinal Stromal Tumors (GIST)

Introduction and Nomenclature

Gastrointestinal stromal tumors (GIST) are a heterogeneous group of mesenchymal tumors of the gastrointestinal (GI) tract with variable clinical behavior (from benign to overtly malignant) believed to arise in most cases from the interstitial cells of Cajal (ICC) or their multipotential precursor cells. ICC are spindle cells with pacemaker activity, which regulate autonomous nerve transmission and intestinal peristalsis (Corless et al. 2011).

GIST can occur throughout the GI tract, most frequently in the stomach (55–60%) and the small intestine (25–30%), and significantly more rarely in the colon-rectum (4–6%) and distal esophagus (<1%). Small numbers of GIST have been reported as primary tumors in the omentum, mesentery, retroperitoneum and in extra-GI locations. From a molecular perspective, GIST are characterized by the presence of usually mutually exclusive activating mutations in the receptor tyrosine kinase (RTK) *KIT* and *PDGFRA* genes, which can be found in ~80% of all GIST cases. Although molecular analysis are becoming increasingly important in the management of GIST patients, the initial diagnosis is usually histologic: GIST can present with spindle or epithelioid morphology, and generally express the immunohistochemical markers CD117 (*KIT*) and/or DOG1 (encoded by *ANO1*) (Blay et al. 2021).

GIST <2 cm in size, termed micro-GIST (<1 cm) or mini-GIST (1–2 cm), are considered putative precursor lesions of larger GIST and are often incidentally discovered. They are generally not resected, as they carry a relatively low individual risk of progression, whereas larger resectable GIST can be cured with surgery. After the discovery of druggable driver mutations, advanced GIST have represented a prototypical solid tumor wherein targeted therapies have proven significantly more effective than conventional chemotherapy. In fact, unresectable and metastatic GIST are in almost all cases treated with tyrosine kinase inhibitors (TKI) that target KIT and/or PDGFRα. In particular, the TKI imatinib represents the first-line treatment for most advanced GIST patients as well as the adjuvant treatment for patients with resected disease at high risk of relapse. Secondary mutations acquired during treatment can cause drug resistance, thus partially limiting treatment success (Casali et al. 2022).

In the past, GIST were classified as GI smooth muscle tumors and GI autonomic nerve or nerve sheath tumors. It is nowadays clear from genetic and immunohistochemical analyses that GIST comprise more than 80% of all mesenchymal tumors of the GI tract, and they include the large majority of tumors previously classified as GI leiomyomas and leiomyosarcomas (Lasota et al. 1999; Lee et al. 2001). Nevertheless, it should be noted that other sarcomas, in particular leiomyosarcomas, can be found in the GI tract and these will be separately covered in the second part of this chapter.

Epidemiology

GIST occur with an estimated incidence of 6–22 per million individuals per year, with differences between geographical areas and over time. The apparent incidence of diagnosed cases might depend on factors such as healthcare availability, number of endoscopic and surgical procedures that give an opportunity to detect incidental GIST, and on true variation in GIST population incidence (Ma et al. 2015; Soreide et al. 2016).

Median age at GIST diagnosis varies between 60 and 65 years, with only 10% of all GIST patients diagnosed before the age of 40 years and less than 1% diagnosed before the age of 18 years. GIST in the adult population are equally distributed between genders, usually present with somatic mutations in *KIT* or *PDGFRA*, and are for the vast majority sporadic in nature (Blay et al. 2021). GIST occurring in children and young adults are more commonly diagnosed in females and in the gastric location, are often lacking driver *KIT* or *PDGFRA* mutations (collectively termed KIT/ PDGFRA wild-type GIST) and can

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be found as part of specific tumor syndromes. Of these, neurofibromatosis 1 (NF1) is the most common, followed by syndromes associated to inactivation of the mitochondrial tumor suppressor gene pathway of the succinate dehydrogenase (SDH) (i.e. the Carney–Stratakis syndrome and the Carney triad), and multifocal familial GIST with inheritable *KIT* or *PDGFRA* mutations (Boikos et al. 2016).

Clinical Presentation and Natural History

The clinical presentation of GIST is the classical presentation of a tumor of the digestive tract, with the most common symptoms being gastrointestinal bleeding, weight loss, and abdominal pain. Importantly, about one third of all GIST is incidentally diagnosed in asymptomatic patients during gastroscopy, abdominal surgery, or radiologic exams performed for an unrelated condition, or by routine clinical examination.

Bleeding results from an ulcerated tumor and it is more commonly insidious and occult, resulting in chronic anemia and associated symptoms. More rarely, acute bleeding manifests as melena, and can lead to a medical emergency. Larger esophageal, intestinal, and rectal GIST can cause symptomatic obstruction, while intussusception is a rare complication. Larger cystic tumors may rupture into the abdominal cavity and cause an acute abdomen. Some patients with larger necrotic, possibly secondarily infected tumors, may have generalized infection-like symptoms such as fever, usually combined with abdominal pain. In advanced cases, signs and symptoms might depend on the presence of metastatic disease.

Metastases more commonly develop in GIST with higher mitotic activity, typically within 1–2 years from presentation, often even after apparently complete surgery. Tumours with lower mitotic activity and smaller dimensions metastasize less frequently, and this may often be after a considerable delay that can be of 10 years or more after surgery. Risk assessment in localized resected GIST has been evaluated with several classifications over the years and will discussed in a separate paragraph.

Common metastatic sites for GISTs are the omentum, the mesentery, and the other peritoneal surfaces. For this reason, primary or metastatic GIST can often simulate a gynecologic cancer. Liver metastases are also common for GIST of any origin, and the involvement varies from solitary or multiple nodules to diffuse involvement in advanced cases. Lung metastases are exceptionally rare in GIST, in contrast to other types of soft tissue sarcomas. Also, histologically verifiable lymph node metastases are extremely rare. Bone metastases (especially the axial skeleton) and peripheral soft tissue metastases can also rarely occur. The soft tissue of abdominal wall represents an exception, as it is affected more frequently.

Diagnosis

The strategy to carry out a diagnostic biopsy for morphologic and molecular diagnosis depends on the location and size of the tumor and clinical circumstances. Tumors that ulcerate gastrointestinal mucosa can often be reached via endoscopic biopsy, except when in the jejunum or ileum. Gastric tumors located beyond the mucosa can be reached via ultrasound-guided endoscopic biopsy. Ultrasound or CT-guided biopsies are used for larger abdominal tumors or for metastatic lesions. Importantly, percutaneous biopsies have not been associated to a significant risk of dissemination or relapse. Smaller tumors that are tentatively identified as GIST are definitively diagnosed in the excision specimen. Saving multiple samples of tissue in a tumor bank should be considered whenever possible, because this will facilitate subsequent molecular analysis (Blay et al. 2021; Casali et al. 2022).

Staging procedures for GIST patients usually include contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis. Magnetic resonance imaging (MRI) may be an alternative procedure, especially for rectal GIST, and (Choi et al.) 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) may be useful when early evaluation of the tumor response to treatment is useful. Radiologically, the most common imaging appearance of primary GIST is a mass arising from the gastrointestinal wall and projecting into the abdominal cavity. Less commonly, GISTs are intramural masses or intraluminal polyps. In all morphologies, GIST typically have smoothly marginated outer contours. As they enlarge, focal ulceration may occur on the mucosal surface overlying the tumor. Small GIST are typically homogeneous on imaging studies. In contrast, larger GIST are more commonly heterogeneous on imaging studies because of degenerative, necrotic, and hemorrhagic regions within the tumor (King 2005).

Histologically, GIST can be relatively reliably identified by their characteristic morphologic features by an experienced pathologist. Approximately 70% of GIST are spindle cell tumors, consisting of cells with fibrillary cytoplasm and ovoid nuclei; ~20% has epithelioid morphology, with rounded cells and occasional focal pleomorphism; the remaining 10% has a mixed phenotype. The morphology is partially dependent on the tumor location as well, with intestinal GIST being in the vast majority of cases spindle cell tumors. The diagnosis of GIST is usually confirmed by the immunohistochemical demonstration of CD117 (KIT) positivity. Detection of CD117 positivity in mast cells and ICC and its absence in normal smooth muscle and fibroblasts serve as excellent internal controls to validate the sensitivity and specificity of KIT immunostaining. CD117 is absent in most other tumors considered in the differential diagnosis of GIST; however, it should be considered that melanoma, mastocytoma, Ewing sarcoma, and angiosarcoma are among non-GISTs that can be KIT-positive. Additional immunohistochemical markers, such as DOG1 (positive in ~90–95% of all cases) and CD34 (positive in ~70% of all cases), are also often used. These markers are particularly important in some *PDGFRA* mutant and KIT/PDGRA wild-type GIST, wherein CD117 positivity can be weak or absent altogether. Finally, mutational analysis can further confirm the diagnosis of GIST and simultaneously provide useful information for treatment selection (Espinosa et al. 2008; Miettinen et al. 2000).

Pathophysiology and Molecular Subgroups of GIST

The etiology and pathophysiology of GIST are poorly understood, with no clear environmental risk factor contributing to the development of the disease. As *KIT* and *PDGFRA* mutations are also found in small benign micro- and mini-GIST, they likely represent early pathogenic events that are necessary although not sufficient for the full malignant transformation of ICC (Blay et al. 2021).

Additional genomic evets contributing to the transformation in malignant GIST include loss or inactivation of several cell cycle regulators as well as of the tumor suppressors MAX and *DPDC5* (Heinrich et al. 2019; Pang et al. 2019; Schaefer et al. 2017). Other downstream events crucially important in the pathogenesis of GIST are considered to be the overexpression of the transcription factor ETV1 and the upregulation of the MEK-MAPK and PI3K pathways (Bosbach et al. 2017; Chi et al. 2010).

As already anticipated, mutually exclusive molecular driver events can be identified in more than 95% of all GIST cases. These alterations define subgroups of GIST with diverging and overlapping pathologic, biological, and clinical characteristics. The largest group is represented by GIST harboring *KIT* and *PDGFRA* mutations, respectively found in 60–70% and 10–15% of all GIST patients. The mutations cause changes in the amino acid sequence of the KIT or PDGFRα proteins by substituting one amino acid for another, or by deleting or adding new amino acid residues. The mutant proteins are presumed to abnormally activate the KIT and PDGFRα signal transduction pathway, which under normal circumstances is activated by growth factor signals. Because sensitivity to targeted kinase inhibitor treatment (especially for imatinib) depends on *KIT* or *PDGFRA* mutation type, mutation analysis is helpful in tailoring the therapy for individual patients. Also, detection of GIST-specific *KIT* or *PDGFRA* mutations is useful in verifying the diagnosis in cases that are negative for CD117 expression.

The remaining KIT/PDGFRA wild-type GIST include those carrying genetic or epigenetic alterations in SDH family genes (~10% of all GIST), and those significantly rarer with alterations in RAS family genes (e.g. *NF1* and *BRAF*) or gene fusions (Figure 1). The main characteristics of each molecular subtype will be summarized below (Boikos et al. 2016).

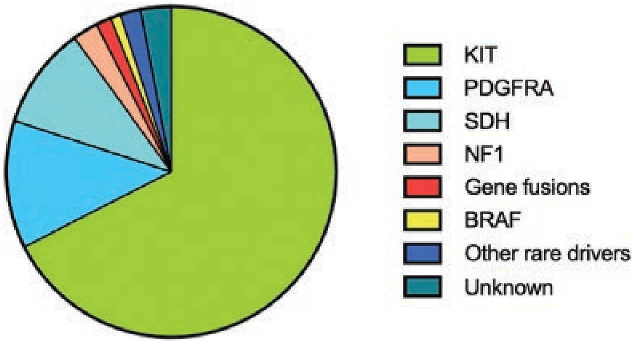

Figure 1 Frequency of the different molecular subgroups of GIST.

KIT

KIT is a transmembrane tyrosine kinase receptor structurally related to the colony stimulating factor 1 receptor and PDGFRs, with kinase activity induced following dimerization upon binding of its ligand, stem cell factor (SCF). From a structural perspective, KIT is characterized by the presence of an extracellular domain responsible of ligand binding and receptor dimerization (encoded in exons 1 to 9); a single transmembrane helix (exon 10); a cytosolic juxtamembrane domain with autoinhibitory function (exon 11); and a cytoplasmic kinase domain split in an ATP-binding domain (including exons 13 and 14) and an activation loop domain (including exons 17 and 18) (Lennartsson and Ronnstrand 2012).

KIT mutations are found in 60–70% of all GIST patients and include in frame deletions, deletions-insertions and insertions, and point mutations. About 85% of all primary *KIT* mutations are found in exon 11, with approximately half of these mutations represented by deletions of the *KIT* codons 557–558. The next most frequent primary mutation is the duplication insertion of codons 502–503 in exon 9, responsible of ~10% of all *KIT* mutations. Primary mutations in exons 13 (exceptionally in exon 14) and in exon 17 are significantly rarer (Figure 2).

GIST with exon 11 and exon 9 primary mutations are significantly different in terms of biology, clinical behavior, and response to treatments (Napolitano et al. 2022). From a molecular perspective, mutations in exon 11 activate KIT independently of SCF and the mutated protein is localized for the most part intracellularly, whereas KIT with exon 9 mutations maintain partial ligand sensitivity and localization to the cell membrane (Shi et al. 2016).

Clinically, GIST with *KIT* exon 11 mutations can be found in any anatomical site, whereas GIST with exon 9 mutations are more frequently found in the intestine, where they represent up to 25% of all diagnosed GIST. Moreover, in the advanced setting *KIT* exon 11 mutant GIST usually respond well to treatment with first-line imatinib, whereas exon 9 mutant have reduced sensitivity. In these patients, progression-free survival (PFS) can be improved with an increased dose of imatinib (Gastrointestinal Stromal Tumor Meta-Analysis, 2010). Of

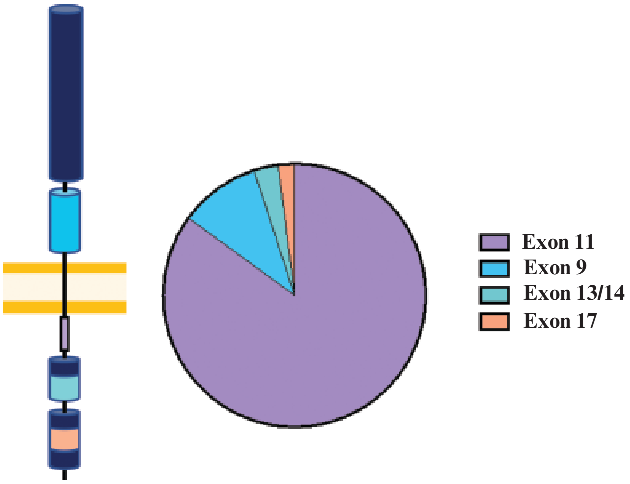

Figure 2 Frequency and molecular localization of the different primary *KIT* mutations in GIST.

note, in a retrospective series of *KIT* exon 9 mutant patients treated the adjuvant setting, a higher dose of imatinib was not associated to a significant benefit over the standard dose (Vincenzi et al. 2021). For second-line sunitinib, the PFS of patients with *KIT* exon 9 mutations is longer than that of patients with exon 11 mutations (Heinrich et al. 2008).

From a prognostic perspective, for *KIT* exon 11 mutant GIST, the presence of the deletion of codons 557–558 has been associated to more aggressive clinicopathological features and increased risk of relapse after surgery compared to the presence of missense mutations (Martin et al. 2005). A negative prognostic impact of *KIT* exon 9 mutation has also been proposed, but this is still debated as GIST in the small bowel are prognostically less favorable compared to those in other locations regardless of the mutational status (Napolitano et al. 2022).

Mutations in exons 13/14 and in exon 17 are significantly more common as secondary resistance mutations, and their prognostic and predictive role when found as primary mutations is poorly defined (Lasota et al. 2008).

Germline mutations in *KIT* have been described in ~25 families. The syndrome is transmitted in an autosomal dominant pattern, and these patients typically develop multiple or sometimes diffuse GIST, usually in middle age, and usually in the stomach or small intestine. Other signs of KIT activation can be present, including cutaneous hyperpigmentation, mastocytosis, and dysphagia. Prognosis varies, and many patients live can long for a long time with the disease. Experience with imatinib treatment in familial GIST is very limited (Brodey et al. 2022; Meir et al. 2021).

PDGFRA

PDGFRα is a transmembrane receptor structurally and functionally related to KIT. Primary mutations in *PDGFRA* are mutually exclusive with *KIT* mutations, usually occur in gastric GIST and more rarely in the small intestine. Some of these tumors have weak or no detectable CD117 expression (Heinrich et al. 2003).

A majority of *PDGFRA* mutant GIST have a favorable prognosis reflecting the prognosis of gastric GIST. The most common *PDGFRA* mutations (~80% of the total) are found in exon 18, which encodes for the activation loop of the kinase domain. The Asp842Val (D842V) substitution is most frequent. While most indels in exon 18 results in imatinib-sensitive *PDGFRA* mutants, D842V-mutant GIST are resistant to imatinib. In fact, the D842V substitution can be also acquired during treatment with imatinib as a secondary resistance mutation. *PDGFRA* exon 12 (juxtamembrane domain) mutations are relatively rare and are expected to be imatinib sensitive. *PDGFRA* exon 14 mutations (ATP-binding domain) have been reported in a few cases, and data on their sensitivity to imatinib are inconclusive (Blay et al. 2021; Corless et al. 2005).

Less than 10 families with germline *PDGFRA* mutations have been described so far. The so called *PDGFRA*-mutation syndrome is characterized by one or more of the following: multiple, stomach-restricted GIST without diffuse ICC hyperplasia; inflammatory fibroid polyps; other unique phenotypic characteristics due to diffuse PDGFRα activation (Manley et al. 2018; Ricci et al. 2015).

SDH

GIST with alterations in components of the SDH enzyme (collectively known as SDH-deficient GIST) are the most common subtype of KIT/ PDGFRA wild-type GIST. They manifest predominantly in females and at a young age. They arise almost exclusively in the stomach, are often multifocal and with epithelioid morphology, and tend to metastasize to the locoregional lymph nodes and liver. Despite metastases, many patients survive a long time with the disease. From a diagnostic perspective, SDH-deficient GIST are characterized by a negative immunohistochemistry for SDHB. Approximately 50% of the SDH-deficient GIST are caused by hypermethylation of the *SDHC* promoter locus, 30% by *SDHA* mutations, and the remaining 20% by mutations in *SDHB*, *SDHC*, *SDHD* (Pitsava et al. 2021).

SDH-deficient GIST can be sporadic in nature, or associated to two tumor syndromes, the Carney triad (CT, OMIM #604287) and the Carney–Stratakis syndrome (CSS, OMIM #606864). CT is a nonfamilial tumor syndrome characterized by the combination of gastric GIST, pulmonary chondroma (hamartoma), and paraganglioma. The median age of onset is 18 years, and there may be a long time span between the appearances of the different components. There is a strong female predominance (85%). Recent evidence support mosaic constitutional epigenetic inactivation of the *SDHC* promoter locus as the cause of CT. CSS is characterized by the presence of

GIST and paraganglioma, it affects both males and females during childhood or adolescence. CSS is caused by germline inactivating mutations in *SDHB*, *SDHC*, and *SDHD* and, more rarely, *SDHA* (Boikos et al. 2016; Dwight et al. 2013; Gourinat et al. 2015; Pasini et al. 2008; Pitsava et al. 2021).

NF1

NF1 patients have a significant predilection to GIST (risk increased by 100–200-fold compared with non-NF1 patients), and GIST are the most common GI mesenchymal tumors in these patients, outnumbering nerve sheath tumors. The NF1-associated GIST typically occur in duodenum, jejunum, and ileum and only rarely in the stomach or colon. They occur in slightly younger patients than sporadic GIST, are often multiple, including minimal GIST precursors, and are accompanied by diffuse Cajal cell hyperplasia. The course is indolent in a majority of cases, although 10–15% of the patients have mitotically active and clinically malignant GIST, more often so in the duodenum. Morphologic features of NF1-associated GIST are similar to those of sporadic intestinal GIST, and they usually positively stain for CD117. In NF1-associated GIST, the mutation in the *NF1* gene is germline and somatic *KIT* and *PDGFRA* mutations are absent (Andersson et al. 2005; Miettinen et al. 2006).

Other KIT/PDGFRA Wild-type GIST

Other rare driver mutations reported in wild-type GIST include activating mutations in *BRAF* or gene fusions involving *NTRK3* or *FGFR1*. The identification of these alterations is becoming increasingly important due to the development of effective targeted therapies (Agaram et al. 2008; Brenca et al. 2016; Napolitano et al. 2021).

Management of Localized GIST

Surgery

Approximately 80% of patients presenting with GIST have primary localized disease without metastasis, when major sequelae to resection are not expected. For them, complete surgical resection is the standard of care and offers the only chance of cure. Large, localized tumors or those challenging to resect because of their location may require neoadjuvant therapy, if the tumor harbors a mutation sensitive to available TKIs. Importantly, while gastric micro- and mini-GIST can undergo surveillance, non-gastric GIST should always be characterized and treatment considered. Laparoscopic resection can be performed by experienced surgeons, and it is especially useful for small gastric GIST (Casali et al. 2022).

Typically, a wedge or segmental resection of the organ from which a GIST has arisen is sufficient. This is because GIST grow exophytically from the gastrointestinal tract and do not usually spread within the bowel wall. Unlike gastrointestinal adenocarcinomas, GIST often just displace adjacent vital structures and do not invade them. Nevertheless, when tumor adherence to nearby structures does occur, partial resection of the involved organs in an *en-bloc* fashion may be necessary to achieve tumor clearance. The overall goal of surgery should be to achieve gross tumor clearance with negative microscopic margins (R0), whenever possible. In patients with low-risk GIST in unfavorable locations, a microscopically positive margin (R1) can be accepted, as R1 resection has not been formally associated with a worse overall survival. On the contrary, intraoperative tumor rupture should be avoided as it is associated to a considerably higher risk of relapse (Gronchi et al. 2020).

Importantly, lymphadenectomy is not routinely performed, as GIST do not usually metastasize to regional nodes. SDH-deficient GIST, which are often multifocal and involve regional nodes, represent an exception. In these cases, resection should include pathologic lymph nodes if present, and it should be performed limiting the extent of gastric resection (Weldon et al. 2017).

Patients with resected GIST are assessed for their risk of recurrence and, in presence of imatinib-sensitive mutations, they are offered adjuvant treatment with imatinib mesylate 400 mg daily for 36 months if their risk of relapse is considered high (i.e. >50%). Ongoing studies are evaluating a longer duration of the adjuvant treatment in patients at higher risk of recurrence. In the case of *KIT* exon 9 mutations, the benefit of a higher dose of imatinib in the adjuvant setting has not been convincingly proven. Imatinib can also be offered in the neoadjuvant setting to improve tumor resectability or allow for more conservative surgical management. In these cases, surgery is usually performed after 12 months of treatment, or sooner at plateaux of radiological response, and the combined duration of the neoadjuvant and adjuvant treatment is 36 months (Casali et al. 2022; Vincenzi et al. 2021).

Following surgery, the current guidelines advocate for patients with intermediate/high-risk GIST a follow up with CT or MRI scans of the abdomen and pelvis with intravenous contrast every 3–6 months during the first 5 years after resection depending on the individual risk of relapse and yearly thereafter. For low-risk tumors, the usefulness of a routine follow-up is not known, and it could be carried out with scans every 6–12 months for 5 years. Very low-risk GIST probably do not require routine follow-up, although the risk is not zero (Casali et al. 2022).

Risk Assessment

The prognosis of GIST is highly variable, and a number of risk assessment tools have been developed to stratify patients with resected GIST based on their risk of developing local or distant recurrence. These tools are based on the most well-characterized prognostic factors identified in GIST, namely tumor

Table 1 Risk assessment table. Adapted from Miettinen and Lasota (2006).

Tumor parameters		Risk of recurrence			
Size	**Mitotic rate (per 50 high power fields)**	**Gastric GIST**	**Jejunal and Ileal GIST**	**Duodenal GIST**	**Rectal GIST**
≤2 cm	≤5	0% none	0% none	0% none	0% none
>2 cm ≤5 cm		1.9% very low	4.3% low	8.3% low	8.5% low
>5 cm ≤10cm		3.6% low	24% moderate	34% high **	57% high **
>10 cm		12% moderate	52% high		
≤2 cm	>5	0% *	50% *	N/A	54% high
>2 cm ≤5 cm		16% moderate	73% high	50% high	52% high
>5 cm ≤10cm		55% high	85% high	86% high **	71% high **
>10 cm		86% high	90% high		

* denotes tumor categories with very few cases

** combined groups because of small number of cases

location, dimension, mitotic count. The most widely used classification, developed by Miettinen and Lasota, categorizes the risk of recurrence in four groups (very low, low, medium, high). As a rule, gastric location, a largest dimension < 5 cm and a mitotic count < 5 mitosis/50 high power fields (HPFs) or 5 mitosis/5 mm^2 are associated to a lower risk of recurrence (Table 1).

More recently, contour maps have been developed, which evaluate tumor dimension and mitotic count as a continuous rather than categorical variable, and also include intraoperative tumor rupture in their models (Joensuu et al. 2012; Miettinen and Lasota 2006).

Knowledge Gap

- Additional but less documented prognostic markers are Ki67 (MIB1) labelling index and expression of p53. Furthermore, the specific contribution to the risk of recurrence of specific driver mutations, such as *KIT* exon 9 or *KIT* exon 11 deletion of the codons 557–558, is highly debated.

While the prognostic impact of tumor dimension and mitotic count is easy to reconcile, it is more difficult to explain the reasons why intestinal GIST behave more aggressively than gastric GIST with similar tumor size and mitotic rate. The biologic background of this is largely unknown, although differences in gene expression profiles of gastric versus small intestinal GIST have been noted (Hemming et al. 2021).

The expected prognosis in different categories is clinically relevant, as it is used to select patients at high risk of relapse possibly requiring adjuvant treatment and may offer guidance for surveillance strategies.

The treatment of localized imatinib-sensitive GIST can be summarized in the following algorithm (Figure 3).

Management of Advanced GIST

Systemic treatment of advanced GIST with conventional sarcoma chemotherapy has generally been ineffective. Targeted therapies with tyrosine kinase inhibitors (TKIs) represent the standard of care in metastatic and unresectable GIST. In many cases, tumors will develop resistance associated to the development of secondary mutations in the same RTK genes. Other mechanisms of resistance depend however on adaptive upregulation of other oncogenic pathways.

Surgery and Local Therapies in Advanced GIST

Local therapies are increasingly finding space in the management of advanced GIST patients. When discussed within expert multidisciplinary tumor boards, they can be offered in different settings and with different goals.

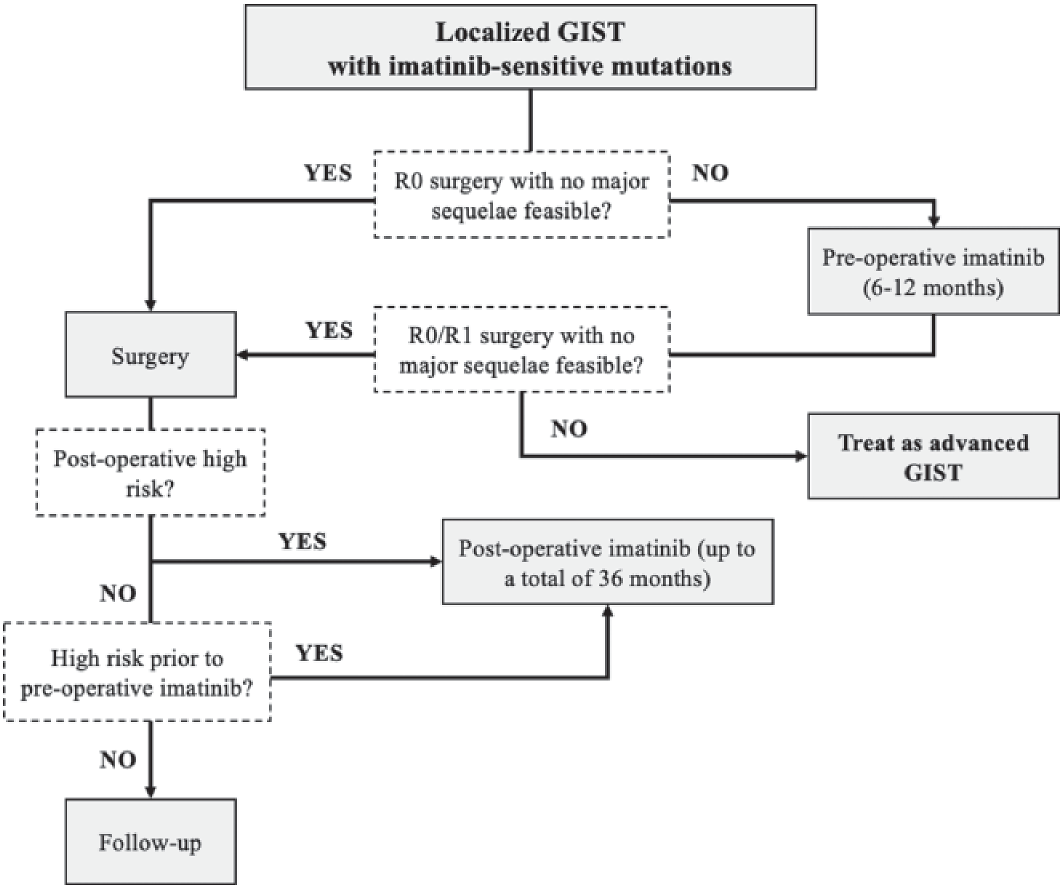
Localized GIST with imatinib-sensitive mutations
R0 surgery with no major sequelae feasible?
YES
NO
Pre-operative imatinib (6-12 months)
Surgery
YES
R0/R1 surgery with no major sequelae feasible?
NO
Treat as advanced GIST
Post-operative high risk?
YES
Post-operative imatinib (up to a total of 36 months)
NO
High risk prior to pre-operative imatinib?
YES
NO
Follow-up

Figure 3 Treatment algorithm of localized GIST patients with imatinib-sensitive mutations.

Patients with low burden of disease responding to imatinib or other TKIs (in particular, those with metastatic disease limited to the liver) could be considered for surgery or other local treatments to residual disease.

Other cases wherein surgery and local therapies are considered are the treatment of:

- symptomatic lesions, as in the case of radiotherapy for bone metastases,
- oligo-progressive metastases, to treat a TKI-resistant clone of disease and defer the change of systemic treatment,
- metastasis with intralesional hemorrhage, fistulation, or causing bowel obstruction.

First-line Treatment

The first-line treatment of GIST patients depends on the mutational status of the disease. GIST with imatinib-sensitive primary mutations (almost all the most common primary *KIT* and *PDGFRA* mutations, except for the *PDGFRA* D842V mutation) are treated with imatinib. Patients who have a small tumor burden at imatinib initiation survive longer than those who have a large burden, which lends support to early initiation of imatinib therapy for GIST patients who are diagnosed with sensitive disease. KIT/PDGFRA wild-type GIST are known to be poorly sensitive to imatinib and ongoing studies are exploring whether other large spectrum TKIs such as regorafenib might have a higher efficacy in this population. Overall, only 10–15% of all patients have a GIST that is primarily resistant to imatinib (Casali et al. 2022).

Imatinib-sensitive GIST are usually treated with a dose of 400 mg once daily. Food has no relevant impact on the rate or extent of imatinib bioavailability, and because imatinib may cause local irritation, it is taken with food. The drug is primarily metabolized in the liver by the cytochrome P450 (CYP) 3A4 or CYP3A5 and has a fecal to urinary excretion ratio is approximately 5:1 (Peng et al. 2005).

Of all GIST patients carrying imatinib-sensitive mutations, approximately 60–80% will achieve a partial response (PR) during treatment, and another 20–30% will have stable disease

(SD) as best response. The presence of a *KIT* exon 11 is associated to a higher likelihood of response to imatinib, whereas GIST with exon 9 can display primary resistance and are less likely to respond. Importantly, patients with SD as best response achieve similar overall survival to patients with a radiological PR. The median response duration of advanced GIST to imatinib treatment is ~24 months, although some patients have shown responses lasting over 5 years, without development of any significant resistance. The presence of *KIT* exon 11 mutation is also associated with a longer median time to imatinib failure as compared to exon 9 mutation (Blanke et al. 2008a). The use of a higher dose of imatinib (e.g., 800 mg daily) has not been associated to better outcomes in *KIT* exon 11 mutated GIST patients, and it is therefore not recommended as an initial treatment in this population. On the other hand, the use of a higher dose of imatinib was associated to a longer PFS in patients with *KIT* exon 9 mutation. Based on these results, imatinib at a dose of 800 mg daily can be offered, whenever national or local policies allow it, as a front-line treatment for patients with *KIT* exon 9 GIST or upon progression to the standard dose of imatinib in presence in patients with GIST carrying other imatinib-sensitive mutations (Casali et al. 2022; Gastrointestinal Stromal Tumor Meta-Analysis Group 2010).

Tumor response to imatinib is usually monitored with CT or sometimes with MRI. The median time to radiological response is 3–4 months when response to imatinib is assessed using conventional response criteria that are based on tumor volume reduction. Patients may obtain subjective benefit within only a few days after starting treatment, which for this reason should be started at the earliest time possible in symptomatic patients, even in those with a poor performance status. No study has evaluated the optimal frequency of response evaluation examinations, which is currently unknown. In clinical practice the first follow-up CT is often carried out 2–3 months after initiation of imatinib, and the subsequent evaluations at approximately 3-month intervals. Metabolic imaging with FDG-PET may occasionally help in the clinical decision-making, as a diminished uptake of FDG in a PET scan may be found within a few hours or days after initiation of imatinib treatment in sensitive patients (Stroobants et al. 2003).

Responding liver metastases characteristically become hypodense on CT or MR imaging following initiation of imatinib treatment. This is due to cell-rich tumor tissue being replaced by hyaline degeneration. Hypodense GIST metastases are better delineated and more easily detected in a CT scan than the denser untreated GIST lesions, which may result in visualization of a greater number of small liver lesions in a CT scan or MRI upon treatment (Figure 4). This must not be misinterpreted as tumor progression. FDG-PET may be helpful in making a differential diagnosis between tumor progression and response in problematic cases. Decrease in metastatic lesion density usually heralds response and lesion volume reduction (Choi et al. 2007).

Imatinib is recommended to be administered continuously without planned breaks in its administration. In case of disease progression following interruption, most patients respond to imatinib reintroduction. Interruption of imatinib administration is unlikely to be beneficial, and continuous imatinib with no upper limit for administration duration is the current standard in the treatment of advanced GIST. Since imatinib dose reductions are best avoided, it is important to know how to manage common adverse effects. Many adverse effects are mild to moderate in severity and may not require any specific therapy. The most frequent adverse effects of imatinib are periorbital or leg edema, occasional muscle cramps in fingers and feet, diarrhea, nausea/vomiting, fatigue, and skin rash. Grade 1 or 2 macrocytic anemia, neutropenia and elevation of serum transaminase levels are also common. Periorbital edema may respond to diuretics and muscle cramps to calcium or magnesium supplementation. Imatinib-related nausea may be

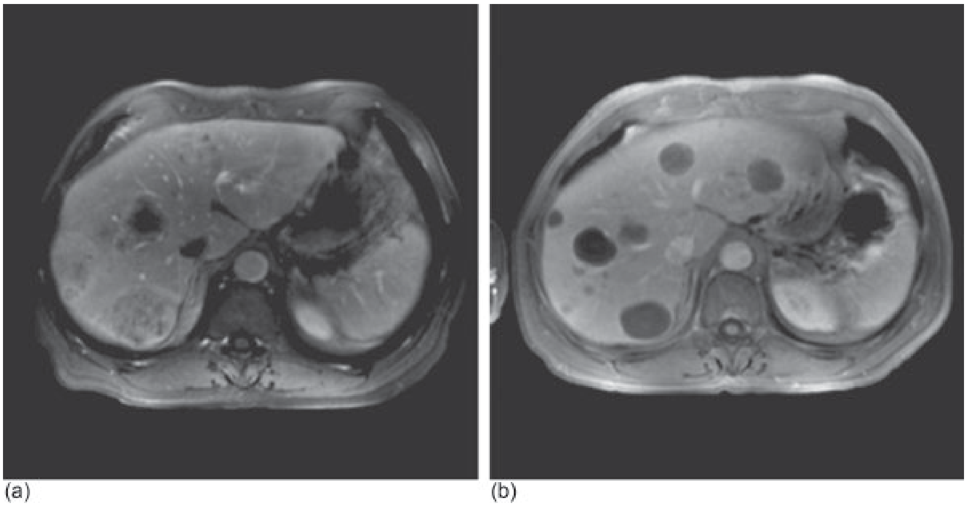

Figure 4 GIST metastases in the liver. (a) Before initiation of imatinib. (b) The metastases have decreased in size and become hypointense following initiation of imatinib administration.

alleviated when the daily imatinib dose is divided and administered twice daily. Imatinib therapy requires close surveillance, especially at the beginning of the treatment and when the patient is elderly or frail, and when multiple concomitant medications cannot be avoided. Generalized skin rash or edema, grade 3 or 4 cytopenias, and dyspnea (may herald interstitial lung disease) require prompt interruption of imatinib administration, and often lead to subsequent dose reduction.

PDGFRA D842V-mutated GIST have been recently shown to respond exceptionally well to the next-generation TKI avapritinib, even at the relatively low doses trialed within a phase I study. In the NAVIGATOR phase I trial, the overall response rate (complete responses, CR, + PR) was 91% and the clinical benefit rate (CR + PR + SD) was 98% with durable responses. The toxicity profile of avapritinib was characterized by gastrointestinal symptoms (nausea and vomiting) and variable neurocognitive toxicity, which might require frequent dose interruptions or reductions (Jones et al. 2021).

KIT/PDGFRA wild-type GIST patients represent a difficult-to-treat population: in SDH-deficient GIST, there may be some benefit from available TKIs, with reports of activity of sunitinib and regorafenib. Patients with GIST carrying *NTRK* rearrangement should be treated with an NTRK inhibitor and those with *BRAF* mutations may benefit from BRAF inhibitors (Casali et al. 2022).

Second-line Treatment

In the event of disease progression on first-line imatinib at 400 mg once daily, dose escalation to 800 mg daily has been proposed as a potential treatment for patients with manageable side effects at the lower dose. About one third of these GIST patients will show radiological stability or response with the higher dose (Blanke et al. 2008b; Verweij et al. 2004). Regulatory constraints may now limit this practice, also considering the availability of further lines of treatment.

The accepted standard of care in second-line is the TKI sunitinib given orally once daily at a 50 mg starting dose in 6-week cycles with 4 weeks on and 2 weeks off treatment, with a median time to tumor progression of approximately 7 months (Demetri et al. 2006). Treatment with sunitinib can be associated to significant side effects, with hypertension and palmar-plantar erythrodysesthesia reported by approximately 50% of all treated patients. A continuous dosing of sunitinib at 37.5 mg can be alternatively considered and might be better tolerated (George et al. 2009).

The activity of sunitinib is significantly influenced by both primary and secondary *KIT* mutations. In particular, the activity of sunitinib was more pronounced in patients carrying primary *KIT* exon 9 mutations (median time to progression of approximately 12 months), as well as in those with secondary *KIT* exon 13 or 14 mutations, rather than exon 17 or 18 mutations (Heinrich et al. 2008; Reichardt et al. 2016).

More recently, in the INTRIGUE trial, the next-generation TKI ripretinib failed to show superiority compared to sunitinib in this setting, despite meaningful clinical activity and improved tolerability compared to sunitinib. Importantly, in the subset of patients with *KIT* exon 9 mutation, sunitinib was significantly superior to ripretinib (Bauer et al. 2022).

Third-line Treatment

Regorafenib at a starting daily dose of 160 mg in a 3 weeks on and 1 week off schedule has activity in GIST patients in third-line, as demonstrated in the GRID trial (Demetri et al. 2013). In this study, the median progression-free survival with regorafenib was 4.8 months, compared to less than one month for placebo. The toxicity profile of regorafenib is similar to the one of sunitinib, with hypertension, palmar-plantar erythrodysesthesia and diarrhea reported in 40–50% of all patients. As for the case of sunitinib, personalized schedules of regorafenib might be better tolerated and associated to good clinical outcomes (Nannini et al. 2021).

Importantly, similar benefits from regorafenib are observed in patients whose tumors harbored primary *KIT* exon 11 or exon 9 mutations, and across various secondary *KIT* mutations (Jeffers et al. 2022).

The randomized Phase 3 VOYAGER trial showed no significant difference in progression-free survival between regorafenib and avapritinib as third-line or later treatment in patients with molecularly unselected, unresectable or metastatic GIST (Kang et al. 2021). Therefore, regorafenib remains the standard of care in this setting.

Fourth-line Treatment

In the pivotal INVICTUS trial, ripretinib at a dose of 150 mg once daily showed meaningful clinical activity in GIST patients in the fourth line of treatment, with a median progression-free survival of 6.3 months and manageable toxicities (Blay et al. 2020). In patients benefitting from ripretinib, intra-patient dose escalation to 150 mg twice daily can be associated to further clinical benefit (George et al. 2021; Zalcberg et al. 2021).

Notably, in this setting ripretinib showed activity across broad mutation subgroups (Bauer et al. 2021), consistent with its novel mechanism of action as a switch-control TKI, specifically developed to target both primary and secondary *KIT* and *PDGFRα* resistance mutations (Goggin et al. 2022).

The treatment of advanced GIST can be summarized in the following algorithm (Figure 5).

Conclusion

Over the last decades, the integration of multiple treatment modalities is becoming increasingly important in the management of GIST patients. Surgery, once limited to the localized setting, is now also part of the integrated management of advanced GIST patients, together with other local therapies.

Historically, GIST has represented the first example of a solid tumor wherein targeted therapies with TKIs has led to dramatic changes in the natural history of the disease, and it continues even today to represent a model to study the impact of secondary mutations in kinases and to develop new and more effective inhibitors.

The key principles of management of GIST are summarized in Table 2.

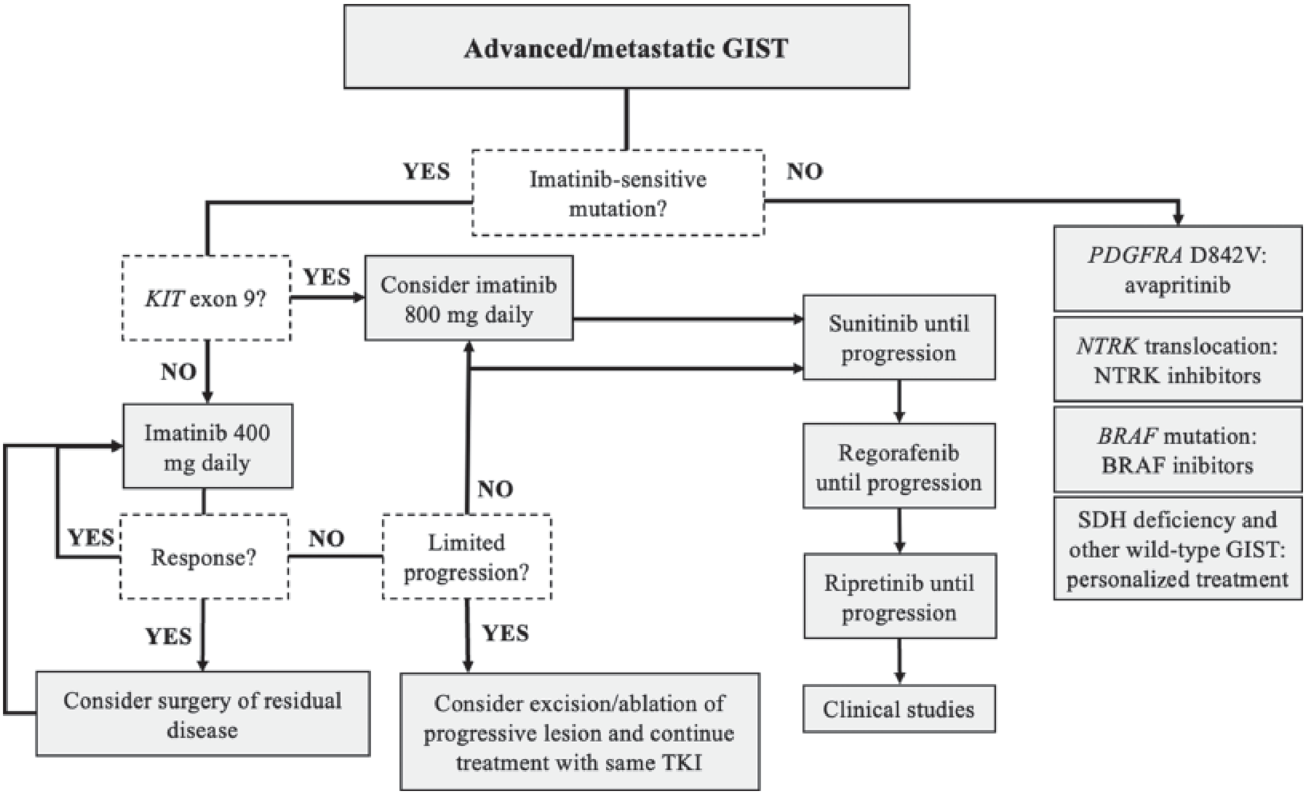
Advanced/metastatic GIST
Imatinib-sensitive mutation?
YES
NO
KIT exon 9?
YES
Consider imatinib 800 mg daily
NO
Imatinib 400 mg daily
Response?
YES
NO
YES
Limited progression?
NO
YES
Consider surgery of residual disease
Consider excision/ablation of progressive lesion and continue treatment with same TKI
Sunitinib until progression
Regorafenib until progression
Ripretinib until progression
Clinical studies
PDGFRA D842V: avapritinib
NTRK translocation: NTRK inhibitors
BRAF mutation: BRAF inibitors
SDH deficiency and other wild-type GIST: personalized treatment

Figure 5 Treatment algorithm of advanced/metastatic GIST patients.

Table 2 Key principles in the management of GIST.

Clinical scenario	Management
Local disease	Complete surgical removal of the tumor with free (usually > 1 cm) margins. Avoid tumor rupture. Consider neoadjuvant treatment with imatinib in presence of GIST with imatinib-sensitive mutations, if R0 surgery with no major sequelae is difficult to achieve. Adjuvant imatinib recommended in case of high-risk tumors with imatinib-sensitive mutations.
Recurrent/metastatic disease; first-line therapy	Imatinib-sensitive mutations: imatinib daily until treatment failure; starting dose is usually 400 mg (900 mg/day can be considered for GIST carrying *KIT* exon 9 mutations). Monitor blood cell counts, blood chemistry and treatment response. Surgical resection of residual tumours of responding patients may be considered in selected cases, but the benefit is unproven. Removal of bleeding, infected or obstructing metastases may be necessary. Avapritinib for patients with *PDGFRA* D842V GIST, if available. Other targeted therapies or clinical trials with novel agents in presence of GIST with imatinib-insensitive mutations.
GIST progresses during imatinib therapy	Check for compliance of taking imatinib – if available, monitor blood levels of imatinib. Consider surgery or local treatments for single growing metastases. Such metastases may harbor a new gene mutation that renders GIST resistant to imatinib. Escalate imatinib dose up to 800 mg/day, if feasible. Second-line: sunitinib. Third-line: regorafenib. Fourth-line: ripretinib. Participation in a clinical trial with novel agents. Palliative surgery or radiation therapy in selected cases.

Other GI Sarcomas

Introduction

Although GIST are by far the most common subtype of soft-tissue sarcoma diagnosed in the GI tract, other GI sarcomas have been described. Given their rarity, their epidemiology is difficult to establish. Moreover, their clinical characteristics and prognosis are significantly influenced by the underlying histology. The most frequently GI sarcomas other than GIST are GI leiomyosarcomas, undifferentiated pleomorphic sarcomas (UPS) and liposarcomas.

GI Leiomyosarcomas

GI leiomyosarcomas are distinguished by GIST based on the immunohistochemical expression of smooth muscle markers and absence of driver mutations. They can be found in any part of the GI tract, and appear to be evenly divided between the stomach, the small intestine, and the colon. They often present with symptoms of obstruction/intussusception and are characterized by a high tendency to metastatic spread despite optimal surgery and poor outcomes (Senapathi et al. 2021; Smrke et al. 2021).

GI Ups

UPS are aggressive undifferentiated sarcomas with poor outcomes. Fewer than 50 cases of GI UPS have been reported in the literature, evenly distributed between gastric and colonic UPS. As for extra-GI UPS, there is a higher incidence in males in their sixth or seventh decade of life. Treatment often included surgery, but recurrence and metastatic spread are frequent (Han et al. 2022; Kabashima et al. 2017; Oguri et al. 2018).

GI Liposarcomas

Primary GI liposarcomas have been described in any part of the GI tract, more frequently in the stomach, in the small intestine, and in the large intestine, less frequently in the esophagus and rectum. Histologically, GI liposarcomas are well-differentiated or de-differentiated liposarcomas characterized by *MDM2* amplification, and compared to those arising in other sites they are more frequently high-grade dedifferentiated tumors and biologically aggressive (Gajzer et al. 2020).

Conclusion

Non-GIST GI sarcomas are exceedingly rare and only case reports or small series have been reported. It is clinically important to be aware of their existence, as they might represent pre-operative differential diagnosis of the more common GI carcinomas and GIST. Whenever possible, pre-operative histological diagnosis is therefore fundamental to accurately plan the treatment. This is particularly important because, although relatively limited information is available on the outcomes of non-GIST GI sarcomas, they are often associated with a poor prognosis.

Key Take Home Messages

- Most gastrointestinal sarcomas are GIST, which are characterized by well-defined histopathological and molecular characteristics, such as mutations in the *KIT* and *PDGFRA* genes.
- Treatment of patients with localized GIST is mainly surgical. Neoadjuvant and adjuvant systemic therapy with imatinib can be respectively considered depending on preoperative surgical risks and postoperative risk of recurrence.
- In the advanced setting, tyrosine kinase inhibitors represent the main treatment. Imatinib should be started as soon as possible in imatinib-sensitive GIST patients, as it is associated to good symptomatic benefit. Locoregional therapies can have an important role in patients with advanced GIST.
- Rare non-GIST gastrointestinal sarcomas include leiomyosarcomas, undifferentiated pleomorphic sarcomas and liposarcomas. Their prognosis is usually poor.

Areas for Further Research

- Prognostic and predictive biomarkers
- Longitudinal non-invasive evaluation of tumor heterogeneity and evolution (e.g., with circulating DNA) to inform therapeutic choices
- Novel therapies for patients without the most common driver mutations and for patients with advanced disease refractory to current therapies

Trusted Websites for Further Reading

- Adult GIST: https://www.cancer.gov/types/soft-tissue-sarcoma/hp/gist-treatment-pdq
- Childhood GIST: https://www.cancer.gov/types/soft-tissue-sarcoma/hp/child-gist-treatment-pdq

References

Agaram, N.P., Wong, G.C., Guo, T. et al. (2008). Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. *Genes Chromosomes Cancer* 47: 853–859.

Andersson, J., Sihto, H., Meis-Kindblom, J.M. et al. (2005). NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. *Am J Surg Pathol* 29: 1170–1176.

Bauer, S., Heinrich, M.C., George, S. et al. (2021). Clinical activity of ripretinib in patients with advanced gastrointestinal stromal tumor harboring heterogeneous KIT/PDGFRA mutations in the phase III INVICTUS study. *Clin Cancer Res* 27: 6333–6342.

Bauer, S., Jones, R.L., Blay, J.Y. et al. (2022). Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial. *J Clin Oncol* 40: 3918–3928 JCO2200294.

Blanke, C.D., Demetri, G.D., Von Mehren, M. et al. (2008a). Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 26: 620–625.

Blanke, C.D., Rankin, C., Demetri, G.D. et al. (2008b). Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol* 26: 626–632.

Blay, J.Y., Kang, Y.K., Nishida, T. et al. (2021). Gastrointestinal stromal tumours. *Nat Rev Dis Primers* 7: 22.

Blay, J.Y., Serrano, C., Heinrich, M.C. et al. (2020). Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 21: 923–934.

Boikos, S.A., Pappo, A.S., Killian, J.K. et al. 2016. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: a report from the national institutes of health gastrointestinal stromal tumor clinic. JAMA Oncol, 2, 922–928.

Bosbach, B., Rossi, F., Yozgat, Y. et al. (2017). Direct engagement of the PI3K pathway by mutant KIT dominates oncogenic signaling in gastrointestinal stromal tumor. *Proc Natl Acad Sci U S A* 114: E8448–E8457.

Brenca, M., Rossi, S., Polano, M. et al. (2016). Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. *J Pathol* 238: 543–549.

Brodey, A., Kounnis, V., Hawkes, L. et al. (2022). KIT-associated familial GIST syndrome: response to tyrosine kinase inhibitors and implications for risk management. *Oncologist* 5: 615–620.

Casali, P.G., Blay, J.Y., Abecassis, N. et al. (2022). Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 33: 20–33.

Chi, P., Chen, Y., Zhang, L. et al. (2010). ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. *Nature* 467: 849–853.

Choi, H., Charnsangavej, C., Faria, S.C. et al. (2007). Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 25: 1753–1759.

Corless, C.L., Barnett, C.M., and Heinrich, M.C. (2011). Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer* 11: 865–878.

Corless, C.L., Schroeder, A., Griffith, D. et al. (2005). PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol* 23: 5357–5364.

Demetri, G.D., Reichardt, P., Kang, Y.K. et al. (2013). Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 381: 295–302.

Demetri, G.D., Van Oosterom, A.T., Garrett, C.R. et al. (2006). Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 368: 1329–1338.

Dwight, T., Benn, D.E., Clarkson, A. et al. (2013). Loss of SDHA expression identifies SDHA mutations in succinate dehydrogenase-deficient gastrointestinal stromal tumors. *Am J Surg Pathol* 37: 226–233.

Espinosa, I., Lee, C.H., Kim, M.K. et al. (2008). A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. *Am J Surg Pathol* 32: 210–218.

Gajzer, D.C., Fletcher, C.D., Agaimy, A. et al. (2020). Primary gastrointestinal liposarcoma-a clinicopathological study of 8 cases of a rare entity. *Hum Pathol* 97: 80–93.

Gastrointestinal Stromal Tumor Meta-Analysis Group. (2010). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. *J Clin Oncol* 28: 1247–1253.

George, S., Blay, J.Y., Casali, P.G. et al. (2009). Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. *Eur J Cancer* 45: 1959–1968.

George, S., Chi, P., Heinrich, M.C. et al. (2021). Ripretinib intrapatient dose escalation after disease progression provides clinically meaningful outcomes in advanced gastrointestinal stromal tumour. *Eur J Cancer* 155: 236–244.

Goggin, C., Stansfeld, A., Mahalingam, P. et al. (2022). Ripretinib in advanced gastrointestinal stromal tumors: an overview of current evidence and drug approval. *Future Oncol* 18: 2967–2978.

Gourinat, A.C., O'connor, O., Calvez, E. et al. (2015). Detection of Zika virus in urine. *Emerg Infect Dis* 21: 84–86.

Gronchi, A., Bonvalot, S., Poveda Velasco, A. et al. (2020). Quality of surgery and outcome in localized gastrointestinal stromal tumors treated within an international intergroup randomized clinical trial of adjuvant imatinib. *JAMA Surg* 155: e200397.

Han, X., Zhao, L., Mu, Y. et al. 2022. Undifferentiated high-grade pleomorphic sarcoma of the colon: a rare case report and literature review. BMC Gastroenterol, 22, 115.

Heinrich, M.C., Corless, C.L., Duensing, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 299: 708–710.

Heinrich, M.C., Maki, R.G., Corless, C.L. et al. (2008). Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol* 26: 5352–5359.

Heinrich, M.C., Patterson, J., Beadling, C. et al. (2019). Genomic aberrations in cell cycle genes predict progression of KIT-mutant gastrointestinal stromal tumors (GISTs). *Clin Sarcoma Res* 9: 3.

Hemming, M.L., Coy, S., Lin, J.R. et al. (2021). HAND1 and BARX1 act as transcriptional and anatomic determinants of malignancy in gastrointestinal stromal tumor. *Clin Cancer Res* 27: 1706–1719.

Jeffers, M., Kappeler, C., Kuss, I. et al. (2022). Broad spectrum of regorafenib activity on mutant KIT and absence of clonal selection in gastrointestinal stromal tumor (GIST): correlative analysis from the GRID trial. *Gastric Cancer* 25: 598–608.

Joensuu, H., Vehtari, A., Riihimaki, J. et al. (2012). Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol* 13: 265–274.

Jones, R.L., Serrano, C., Von Mehren, M. et al. (2021). Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: long-term efficacy and safety data from the NAVIGATOR phase I trial. *Eur J Cancer* 145: 132–142.

Kabashima, A., Kimura, K., Sanefuji, K. et al. 2017. A case of primary gastric undifferentiated high-grade pleomorphic sarcoma diagnosed with chief complaint of fever: a case report and literature review. Surg Case Rep, 3, 41.

Kang, Y.K., George, S., Jones, R.L. et al. (2021). Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: a randomized, open-label phase III study. *J Clin Oncol* 39: 3128–3139.

King, D.M. (2005). The radiology of gastrointestinal stromal tumours (GIST). *Cancer Imaging* 5: 150–156.

Lasota, J., Corless, C.L., Heinrich, M.C. et al. (2008). Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. *Mod Pathol* 21: 476–484.

Lasota, J., Jasinski, M., Sarlomo-Rikala, M. et al. (1999). Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. *Am J Pathol* 154: 53–60.

Lee, J.R., Joshi, V., Griffin, J.W., Jr. et al. (2001). Gastrointestinal autonomic nerve tumor: immunohistochemical and molecular identity with gastrointestinal stromal tumor. *Am J Surg Pathol* 25: 979–987.

Lennartsson, J. and Ronnstrand, L. (2012). Stem cell factor receptor/c-Kit: from basic science to clinical implications. *Physiol Rev* 92: 1619–1649.

Ma, G.L., Murphy, J.D., Martinez, M.E. et al. (2015). Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev* 24: 298–302.

Manley, P.N., Abu-Abed, S., Kirsch, R. et al. (2018). Familial PDGFRA-mutation syndrome: somatic and gastrointestinal phenotype. *Hum Pathol* 76: 52–57.

Martin, J., Poveda, A., Llombart-Bosch, A. et al. (2005). Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). *J Clin Oncol* 23: 6190–6198.

Meir, M., Maurus, K., Kuper, J. et al. (2021). The novel KIT exon 11 germline mutation K558N is associated with gastrointestinal stromal tumor, mastocytosis, and seminoma development. *Genes Chromosomes Cancer* 60: 827–832.

Miettinen, M., Fetsch, J.F., Sobin, L.H. et al. (2006). Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. *Am J Surg Pathol* 30: 90–96.

Miettinen, M. and Lasota, J. (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 23: 70–83.

Miettinen, M., Sobin, L.H., and Sarlomo-Rikala, M. (2000). Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). *Mod Pathol* 13: 1134–1142.

Nannini, M., Rizzo, A., Nigro, M.C. et al. (2021). Standard versus personalized schedule of regorafenib in metastatic gastrointestinal stromal tumors: a retrospective, multicenter, real-world study. *ESMO Open* 6: 100222.

Napolitano, A., Ostler, A.E., Jones, R.L. et al. (2021). Fibroblast growth factor receptor (FGFR) signaling in GIST and soft tissue sarcomas. *Cells* 10.

Napolitano, A., Thway, K., Smith, M.J. et al. (2022). KIT exon 9-mutated gastrointestinal stromal tumours: biology and treatment. *Chemotherapy* 67: 81–90.

Oguri, Y., Cho, H., Oohinata, R. et al. (2018). Aggressive undifferentiated pleomorphic sarcoma of the stomach involving long-term survival: a case report and literature review. *Mol Clin Oncol* 9: 661–665.

Pang, Y., Xie, F., Cao, H. et al. (2019). Mutational inactivation of mTORC1 repressor gene DEPDC5 in human gastrointestinal stromal tumors. *Proc Natl Acad Sci U S A* 116: 22746–22753.

Pasini, B., Mcwhinney, S.R., Bei, T. et al. (2008). Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. *Eur J Hum Genet* 16: 79–88.

Peng, B., Lloyd, P., and Schran, H. (2005). Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 44: 879–894.

Pitsava, G., Settas, N., Faucz, F.R. et al. (2021). Carney triad, carney-stratakis syndrome, 3PAS and other tumors due to SDH deficiency. *Front Endocrinol (Lausanne)* 12: 680609.

Reichardt, P., Demetri, G.D., Gelderblom, H. et al. (2016). Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. *BMC Cancer* 16: 22.

Ricci, R., Martini, M., Cenci, T. et al. (2015). PDGFRA-mutant syndrome. *Mod Pathol* 28: 954–964.

Schaefer, I.M., Wang, Y., Liang, C.W. et al. (2017). MAX inactivation is an early event in GIST development that regulates p16 and cell proliferation. *Nat Commun* 8: 14674.

Senapathi, H., Morada, A., Perry, M. et al. (2021). Prognostic factors in gastrointestinal leiomyosarcomas: an analysis using the surveillance, epidemiology, and end results (SEER) database. *Cureus* 13: e19447.

Shi, X., Sousa, L.P., Mandel-Bausch, E.M. et al. (2016). Distinct cellular properties of oncogenic KIT receptor tyrosine kinase mutants enable alternative courses of cancer cell inhibition. *Proc Natl Acad Sci U S A* 113: E4784–93.

Smrke, A., Benson, C., Strauss, D.C. et al. (2021). Gastrointestinal leiomyosarcoma demonstrate a predilection for distant recurrence and poor response to systemic treatments. *Eur J Surg Oncol* 47: 2595–2601.

Soreide, K., Sandvik, O.M., Soreide, J.A. et al. (2016). Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. *Cancer Epidemiol* 40: 39–46.

Stroobants, S., Goeminne, J., Seegers, M. et al. (2003). 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). *Eur J Cancer* 39: 2012–2020.

Verweij, J., Casali, P.G., Zalcberg, J. et al. (2004). Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 364: 1127–1134.

Vincenzi, B., Napolitano, A., Fiocco, M. et al. (2021). Adjuvant imatinib in patients with GIST harboring exon 9 KIT mutations: results from a multi-institutional European retrospective study. *Clin Cancer Res* 28: 1672–1679.

Weldon, C.B., Madenci, A.L., Boikos, S.A. et al. (2017). Surgical management of wild-type gastrointestinal stromal tumors: a report from the national institutes of health pediatric and wildtype GIST clinic. *J Clin Oncol* 35: 523–528.

Zalcberg, J.R., Heinrich, M.C., George, S. et al. (2021). Clinical benefit of ripretinib dose escalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. *Oncologist* 26: e2053–e2060.

24 Neuroendocrine Neoplasms of the Digestive System

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[Aspects of disease that affect the small bowel are also covered in Chapter 8].

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Introduction

Günter Klöppel & Irene Esposito

General Characteristics

Terminology and Definition

The term "neuroendocrine" characterizes a cell that expresses markers such as synaptophysin and chromogranin A. Using these markers, neuroendocrine cells have been detected almost everywhere in the body and have built up a neuroendocrine cell system across the organs. Despite the uniformity of this cell system, the neoplasms that result from it are heterogeneous. The neuroendocrine neoplasms (NENs) consist of two families, which differ significantly in terms of morphology, genetics, epidemiology, and clinics (Klimstra et al. 2019; Klöppel 2017; Yachida et al. 2021). In the first group of neoplasms, which also bear the name carcinoids, growth and behavior are slower and individually more different than in the second group of neoplasms with their generally much faster growth and more aggressive behavior. Both groups of NENs can develop almost anywhere in the body but are most common in the gastroenteropancreatic and bronchopulmonary system, where 70–90% of all NENs occur (Kasajima et al. 2020).

The denomination "neuroendocrine" derives from the fact that these cells share certain structures and antigens with neural cells. Typical cellular antigens and structures are peptide hormones and/or biogenic amines, which are stored in electron-dense membrane-bound secretory granules. The membranes of these hormone granules contain the protein chromogranin A, which can be readily detected by immunohistochemistry and represents a general neuroendocrine marker with high specificity. Since chromogranin A is released together with the cell-specific hormone into the circulation, it also serves as serum marker for secreting NENs. Another general neuroendocrine marker is synaptophysin, which resides in the membrane of presynaptic-like vesicles that are located with the hormone granules in the cytoplasm of all neuroendocrine cells (Rindi and Wiedenmann 2020). Recently, the panel of highly specific neuroendocrine markers has been extended by a transcriptional factor, called insulinoma-associated protein 1 (INSM1) (Rosenbaum et al. 2015).

NETs and NECs

Since NENs of the digestive system are the most common NENs in the body, they paved the way for an elaborate WHO classification with clinical relevance. The 2019 WHO classification of digestive system NENs distinguishes between well- and poorly differentiated neoplasms. NENs showing a well-differentiated histology and a low proliferation rate are called neuroendocrine tumors (NETs), while NENs displaying a poorly differentiated histology and high proliferation rate are called neuroendocrine carcinomas (NECs) (Klimstra et al. 2019). NETs show organoid growth patterns with solid-nested, trabecular-gyriform, and/or pseudoglandular growth patterns resembling those of non-neoplastic counterparts such as the islets of Langerhans, while NECs lack the similarity with non-neoplastic endocrine structures and are composed of diffuse sheets of neoplastic cells or poorly formed solid cell nests, often interspersed with necrosis. NECs with a diffuse sheet pattern usually represent the small cell subtype, while NECs with poorly formed solid nests are usually ascribed to the large cell subtype.

Since the two NEN families are also recognized in organs outside the digestive system such as the lung, the WHO published a uniform classification framework for all NENs of the body with the aim to improve the understanding and comparability and finally the treatment of these neoplasms (Rindi et al. 2018).

The 2019 WHO classification also includes the category of mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs), formerly referred to as mixed adenoneuroendocrine carcinomas (MANECs) (Table 1). MiNEN is a conceptional approach to a group of tumors that is not really an entity but consists of neoplasms, which, although mostly monoclonal, show a variable mixture of non-neuroendocrine cell elements (i.e., adenocarcinoma or squamous cell carcinoma) with a usually poorly differentiated neuroendocrine component (Klimstra et al. 2019). The WHO classification of digestive system tumors defines MiNENs as neoplasms, in which each component accounts for more than 30% of the tumor cell population.

Grading of NETs

In addition to histological differentiation, proliferative activity characterizes the individual NEN in terms of categorization and prognosis. Grading of the neoplasm's proliferative activity, as assessed by Ki67 index and/or mitotic rate, contributes greatly to

Table 1 WHO classification of digestive neuroendocrine neoplasms.

	Morphological differentiation	Mitotic count/2 mm^2	Ki67-index
NET G1	Well-differentiated	<2	<3%
NET G2	Well-differentiated	2–20	3–20%
NET G3	Well-differentiated	>20	>20%
NEC	Poorly differentiated	>20	>20%
MiNEN	Well or poorly differentiated*	Variable*	Variable*

NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma.
MiNEN: mixed neuroendocrine/non-neuroendocrine neoplasm.
*referred to the neuroendocrine component.

Table 2 Immunohistochemical profile of most common gastroenteropancreatic neuroendocrine neoplasms.

Tumor type	Site	Hormone	Transcriptional factor	Molecular marker
NET	Esophagus	None	None	No aberrant expression of P53, Rb1SST2 Expression common
	Stomach	ECL-histamine*	CDX2$^+$	
	Duodenum	Gastrin, somatostatin, serotonin, PP**	CDX2, islet 1$^+$	
	Ileum	Serotonin	CDX2	
	Appendix	Serotonin, Glucagon***	CDX2	
	Colon	Serotonin	CDX2	
	Rectum$^\#$	Glucagon, PP	Islet 1, SATB2	
	Pancreas	Insulin, glucagon, PP, somatostatin, serotonin, gastrin, various hormones****	Islet 1	
NEC	See NET	None	Aberrant expression possible	Aberrant expression of p53, Rb1SSTR2 Expression uncommon

Abbreviation: NET neuroendocrine tumor, NEC neuroendocrine carcinoma, PP pancreatic polypeptide, SSTR2 somatostatin receptor 2.
$^\#$ chromograninA is rarely expressed.
* VMAT2 as surrogate marker.
** in composite gangliocytoma/neuroma and neuroendocrine tumor (CoGNET), previously known as gangliocytic paraganglioma.
*** in tubular type NET.
****VIP, ACTH, calcitonin.
$^+$ occasionally.

the distinction between NETs and NECs, and to the biologic stratification of NETs. Since nuclear labeling with Ki67 has largely replaced the cumbersome counting of mitoses, the exact assessment of the proportion of Ki67-labeled cells as the basis for the calculation of the Ki67 index has emerged as indispensable for the three-tiered grading of NETs into G1, G2, and G3 (Klöppel and La Rosa 2018, Reid et al. 2015) (Table 1). G3 represents a new category that defines the NETs with Ki67 above 20%. It has no defined upper Ki67 rate limit; however, usually the Ki67 index does not exceed 50%. Most G3 NETs appear to develop from low-grade NETs, since they often manifest themselves as metastases in patients with a prior history of a G1 or G2 NET (Kasajima et al. 2022). NECs as poorly differentiated NENs are not graded, but usually present with Ki67 values between 50% and 90%.

Immunohistochemical Features

The immunohistochemical profile of NENs that is essential to establish the diagnosis includes the expression of cytokeratin, synaptophysin, and chromogranin A (Perren et al. 2017). Labeling for cytokeratin proves the epithelial nature of a NEN in cases where a neuroectodermal tumor such as a paraganglioma must be excluded. Diffuse and intense cytoplasmic expression of synaptophysin and chromogranin A and nuclear staining for INSM1 (Tanigawa et al. 2018) reveals the tumor's neuroendocrine differentiation, the common denominator of NENs. The staining of peptide hormones, of the somatostatin receptor 2A (SSTR2A), or the site-specific transcription factors ISLET-1 and CDX2, is indicated there, where the diagnosis needs it to be complete (Table 2) (Agaimy et al. 2013; Kasajima and Klöppel 2020; Konukiewitz et al. 2018, 2017; Vanoli et al. 2016). p53 and RB1 are highly recommended as markers for the distinction of NETs from NECs (Kasajima et al. 2022).

The immunohistochemical profile of small and large cell NECs includes, akin to NETs, the expression of cytokeratin, synaptophysin, INSM1, chromogranin A, as well as the overexpression/deletion of p53 and/or the loss of nuclear RB1 staining (Table 2). In small cell type NECs, cytokeratin labeling may show a punctuate pattern, and in exceptional cases, cytokeratin labeling can even be lacking. A few NECs also express vimentin. Synaptophysin is typically diffusely but faintly and somewhat patchy expressed, often displaying a dot-like pattern. Chromogranin A is usually focally and scarcely expressed and may even be lacking, since neurosecretory granules, whose membranes contain chromogranin A, are rare in NEC cells. CD56 labels the membranes of NECs broadly, but it should be never the only neuroendocrine marker on which the diagnosis of a NEC is based, since it is highly nonspecific.

Morphogenetic Features

The dichotomy of the morphological features of NETs and NECs is reflected in the genetic profiles of the two groups. The key driver genes of NETs occurring in the upper gastrointestinal tract (stomach, duodenum) are *MEN1* and, in the pancreas, *ATRX* or *DAXX* (de Wilde et al. 2012; Heaphy et al. 2011; Jiao et al. 2011; Marinoni et al. 2014; Scarpa et al. 2017; Asa et al. 2021). The molecular profile of NECs is characterized by *TP53* and *RB1* mutations (Konukiewitz et al. 2018; Yachida et al. 2021, Uccella et al. 2021). The pathogenetic role of *MEN1*, *ATRX*, *DAXX*, and their association with an alternative lengthening of telomeres (ALT) has been especially studied in pancreatic NETs and is discussed below. The molecular features of colonic and rectal NETs are largely not known.

NETs of the ileum have a genetic profile that is unique and not comparable to that of the other GEP-NETs. Ileal NETs rarely show somatic mutations but frequently reveal chromosome 18 deletions (Karpathakis et al. 2016). In addition, many of these tumors have epigenetic changes, which are to some extent linked to the prognosis of the tumors (see subchapter on ileal NETs) (Karpathakis et al. 2016).

The majority of MiNENs are poorly differentiated and composed of large cell NECs and cribriform adenocarcinomas. Genetically, MiNENs are closely related to the respective site-specific adenocarcinomas. So MiNENs of the colon, where most of the MiNENs of the gastroenteropancreatic system occur, show mutations of *KRAS, BRAF*, and *APC*, which are typically seen in the conventional adenocarcinomas of the colon (Jesinghaus et al. 2017). This suggests that the tumorigenesis is closely linked to that of conventional adenocarcinomas.

Prognostic and Predictive Biomarkers

Despite relevant progresses in our understanding of the biology and genetics of NENs, the most relevant prognostic factors remain the disease stage and the tumor grade, which should always be assessed. Biomarkers predictive for therapy response are missing or not largely validated. A recent review about available biomarkers is provided in Bocchini et al. (Bocchini et al. 2020). Entity-specific prognostic and predictive biomarkers will be discussed in detail in the following sections.

References

Agaimy, A., Erlenbach-Wunsch, K., Konukiewitz, B. et al. (2013). ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. *Mod Pathol* 26 (7): 995–1003.

Asa, S.L., La Rosa, S., Basturk, O. et al. (2021). Molecular pathology of well-differentiated gastro-entero-pancreatic neuroendocrine tumors. *Endocr Pathol* 32 (1): 169–191.

Bocchini, M., Nicolini, F., Severi, S. et al. (2020). Biomarkers for Pancreatic Neuroendocrine Neoplasms (PanNENs) Management-An Updated Review. *Front Oncol* 10: 831.

de Wilde, R.F., Heaphy, C.M., Maitra, A. et al. (2012). Loss of ATRX or DAXX expression and concomitant acquisition of the alternative lengthening of telomeres phenotype are late events in a small subset of MEN-1 syndrome pancreatic neuroendocrine tumors. *Mod Pathol* 25 (7): 1033–1039.

Heaphy, C.M., de Wilde, R.F., Jiao, Y. et al. (2011). Altered telomeres in tumors with ATRX and DAXX mutations. *Science* 333 (6041): 425.

Jesinghaus, M., Konukiewitz, B., Keller, G. et al. (2017). Colorectal mixed adenoneuroendocrine carcinomas and neuroendocrine carcinomas are genetically closely related to colorectal adenocarcinomas. *Mod Pathol* 30 (4): 610–619.

Jiao, Y., Shi, C., Edil, B.H. et al. (2011). DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 331 (6021): 1199–1203.

Karpathakis, A., Dibra, H., Pipinikas, C. et al. (2016). Prognostic impact of novel molecular subtypes of small intestinal neuroendocrine tumor. *Clin Cancer Res* 22 (1): 250–258.

Kasajima, A. and Klöppel, G. (2020). Neuroendocrine neoplasms of lung, pancreas and gut: a morphology-based comparison. *Endocr Relat Cancer* 27 (11): R417–R32.

Kasajima, A., Konukiewitz, B., Schlitter, A.M. et al. (2022). An analysis of 130 neuroendocrine tumors G3 regarding prevalence, origin, metastasis, and diagnostic features. *Virchows Arch* 480 (2): 359–368.

Klimstra, D., Klöppel, G., La Rosa, S., et al. (2019). Classification of neuroendocrine neoplasms of the digestive system. In: *WHO Classification of Tumours Digestive System Tumours. WHO Classification of Tumours*, 5e (ed. Board TWCoTE), 16–21. Lyon: IARC Press.

Klöppel, G. (2017). Neuroendocrine neoplasms: dichotomy, origin and classifications. *Visc Med* 33 (5): 324–330.

Klöppel, G. and La Rosa, S. (2018). Ki67 labeling index: assessment and prognostic role in gastroenteropancreatic neuroendocrine neoplasms. *Virchows Arch* 472 (3): 341–349.

Konukiewitz, B., Jesinghaus, M., Steiger, K. et al. (2018). Pancreatic neuroendocrine carcinomas reveal a closer relationship to ductal adenocarcinomas than to neuroendocrine tumors G3. *Hum Pathol* 77: 70–79.

Konukiewitz, B., Schlitter, A.M., Jesinghaus, M. et al. (2017). Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20. *Mod Pathol* 30 (4): 587–598.

Marinoni, I., Kurrer, A.S., Vassella, E. et al. (2014). Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. *Gastroenterology* 146 (2): 453–60 e5.

Perren, A., Couvelard, A., Scoazec, J.Y. et al. (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. *Neuroendocrinology* 105 (3): 196–200.

Reid, M.D., Bagci, P., Ohike, N. et al. (2015). Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies. *Mod Pathol* 28 (5): 686–694.

Rindi, G., Klimstra, D.S., Abedi-Ardekani, B. et al. (2018). A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol* 31 (12): 1770–1786.

Rindi, G. and Wiedenmann, B. (2020). Neuroendocrine neoplasia of the gastrointestinal tract revisited: towards precision medicine. *Nat Rev Endocrinol* 16 (10): 590–607.

Rosenbaum, J.N., Guo, Z., Baus, R.M. et al. (2015). INSM1: a novel immunohistochemical and molecular marker for neuroendocrine and neuroepithelial neoplasms. *Am J Clin Pathol* 144 (4): 579–591.

Scarpa, A., Chang, D.K., Nones, K. et al. (2017). Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature* 543 (7643): 65–71.

Tanigawa, M., Nakayama, M., Taira, T. et al. (2018). Insulinoma-associated protein 1 (INSM1) is a useful marker for pancreatic neuroendocrine tumor. *Medical Mol Morphol* 51 (1): 32–40.

Uccella, S., La Rosa, S., Metovic, J. et al. (2021). Genomics of high-grade neuroendocrine neoplasms: well-differentiated neuroendocrine tumor with high-grade features (G3 NET) and neuroendocrine carcinomas (NEC) of various anatomic sites. *Endocr Pathol* 32 (1): 192–210.

Vanoli, A., La Rosa, S., Klersy, C. et al. (2016). Four neuroendocrine tumor types and the neuroendocrine carcinoma of the duodenum. *Analysis of 203 cases. Neuroendocrinology* 104 (2): 112–125.

Yachida, S., Totoki, Y., Noe, M. et al. (2021). Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system. *Cancer Discov* 12 (3): 692–711.

Esophagus – Stomach – Duodenum

Esophagus

Epidemiology and Pathology

Atsuko Kasajima, Günter Klöppel & Stefano La Rosa

Epidemiology

Esophageal neuroendocrine neoplasms (NENs) are rare, accounting for only 0.04–1% of gastro-entero-pancreatic (GEP) NENs and representing 0.03–0.05% of all esophageal malignancies (Dasari et al. 2017; Giannetta et al. 2019). The mean age at diagnosis is 66 years with a male predominance (Mastracci et al. 2021).

Classification

Esophageal NENs are classified according to the same criteria as the NENs of the digestive system into NETs, NECs of small and large cell type, and MiNENs (Klimstra et al. 2019).

Pathology

NETs of the esophagus are extremely rare and outnumbered by NECs and MiNENs. NETs show the histologic features of well-differentiated NENs. NECs and MiNENs are poorly differentiated carcinomas and usually present as large and ulcerated neoplasms in the lower third of the esophagus (Maru et al. 2008). The non-neuroendocrine component consists of either squamous cell carcinoma or adenocarcinoma.

Prognosis

The overall survival of patients with esophageal NETs ranges from 1 to 23 years and depends on tumor stage, while the prognostic role of proliferative activity is not known due to very limited available information. Esophageal NECs are aggressive with a median overall survival time ranging from 8 to 15 months, with most patients dying within 2 years from the diagnosis. The median survival time of MiNENs is about 20 months (Maru et al. 2008).

Clinical Presentation, Diagnosis, and Staging

The most common presenting symptoms of esophageal NENs are dysphagia, weight loss, pain, and signs related to upper-GI bleeding, such as melena. Incidental diagnosis as well as diagnosis due to metastases (carcinoid syndrome) or paraneoplastic syndromes (especially in NECs) are also possible (Lee et al. 2014).

Diagnosis is usually performed at esophagogastroduodenoscopy, where NENs present as polypoid or nodular elevated masses with smooth surface; ulceration is possible, especially in larger tumors (Ye et al. 2019). Staging is performed via endoscopic ultrasound (EUS), computed tomography (CT), and positron emission tomography/CT (PET/CT) (Giannetta et al. 2019; Tirosh and Kebebew 2018).

Surgical Treatment

Levent Dizdar & Wolfram Trudo Knoefel

Esophageal NENs are characterized by an aggressive biological behavior with early dissemination and poor prognosis, probably reflecting the fact that the predominant histologic subtype is poorly differentiated NECs (Estrozi and Bacchi 2011; Mastracci et al. 2021). Due to its extreme rarity, the optimal treatment, including surgical therapy, is unfortunately not standardized so far (Estrozi and Bacchi 2011; Mastracci et al. 2021). Few data suggest that endoscopic resection is sufficient for well-differentiated esophageal NETs without evidence of nodal or distant metastases or lymphovascular invasion (Lee et al. 2014). Patients with more advanced tumors should be evaluated regarding surgical resection. Several studies suggest that patients with stage I and II disease (according to the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal squamous cell carcinoma) benefit from surgical resection (Deng et al. 2016; Erdem et al. 2020; Wong et al. 2017). However, there are conflicting reports regarding the prognostic benefit and indication for surgical resection in stage III disease (Deng et al. 2016; Erdem et al. 2020; Schizas et al. 2017). Esophageal NECs with distant metastases represent an absolute contraindication to surgical intervention (Garcia-Carbonero et al. 2016).

Regarding surgical procedures, esophageal NENs are resected using the same methods used to treat adenocarcinoma or squamous cell carcinoma of the esophagus. The standard procedure for resection of esophageal NENs should be thoracoabdominal esophagectomy. Depending on the tumor location, this procedure can be performed with a thoracic or cervical anastomosis. The use of minimally invasive techniques, especially for the thoracic part of surgery, is associated with improved postoperative outcomes and quality of life with comparable oncologic results provided adequate experience (van der Sluis et al. 2020).

References

Dasari, A., Shen, C., and Halperin, D. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 3: 1335–1342.

Deng, H.Y., Ni, P.Z., Wang, Y.C. et al. (2016). Neuroendocrine carcinoma of the esophagus: clinical characteristics and prognostic evaluation of 49 cases with surgical resection. *J Thorac Dis* 8 (6): 1250–1256.

Erdem, S., Troxler, E., Warschkow, R. et al. (2020). is there a role for surgery in patients with neuroendocrine tumors of the esophagus? a contemporary view from the NCDB. *Ann Surg Oncol* 27 (3): 671–680.

Estrozi, B. and Bacchi, C.E. (2011). Neuroendocrine tumors involving the gastroenteropancreatic tract: a clinicopathological evaluation of 773 cases. *Clinics (Sao Paulo)* 66 (10): 1671–1675.

Garcia-Carbonero, R., Sorbye, H., Baudin, E. et al. (2016). ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology* 103 (2): 186–194.

Giannetta, E., Guarnotta, V., Rota, F. et al. (2019). A rare rarity: neuroendocrine tumor of the esophagus. *Crit Rev Oncol Hematol* 137: 92–107.

Klimstra, D., Klöppel, G., La Rosa, S. et al. (2019). Classification of neuroendocrine neoplasms of the digestive system. In: *WHO Classification of Tumours Digestive System Tumours. WHO Classification of Tumours*, 5e (ed. Board TWCoTE), 16–21. Lyon: IARC Press.

Lee, C.G., Lim, Y.J., Park, S.J. et al. (2014). The clinical features and treatment modality of esophageal neuroendocrine tumors: a multicenter study in Korea. *BMC Cancer* 14: 569.

Maru, D.M., Khurana, H., Rashid, A. et al. (2008). Retrospective study of clinicopathologic features and prognosis of high-grade neuroendocrine carcinoma of the esophagus. *Am J Surg Pathol* 32 (9): 1404–1411.

Mastracci, L., Rindi, G., Grillo, F. et al. (2021). Neuroendocrine neoplasms of the esophagus and stomach. *Pathologica* 113 (1): 5–11.

Schizas, D., Mastoraki, A., Kirkilesis, G.I. et al. (2017). Neuroendocrine tumors of the esophagus: state of the art in diagnostic and therapeutic management. *J Gastrointest Cancer* 48 (4): 299–304.

Tirosh, A. and Kebebew, E. (2018). The utility of (68) Ga-DOTATATEpositron-emission tomography/computed tomography in the diagnosis, management, follow-up and prognosis of neuroendocrine tumors. *Future Oncol* 14 (2): 111–122.

van der Sluis, P.C., Schizas, D., Liakakos, T., and van Hillegersberg, R. (2020). Minimally invasive esophagectomy. *Dig Surg* 37 (2): 93–100.

Wong, A.T., Shao, M., Rineer, J. et al. (2017). Treatment and survival outcomes of small cell carcinoma of the esophagus: an analysis of the national cancer data base. *Dis Esophagus* 30 (2): 1–5.

Ye, L., Lu, H., Wu, L. et al. (2019). The clinicopathologic features and prognosis of esophageal neuroendocrine carcinomas: a single-center study of 53 resection cases. *BMC Cancer* 19 (1): 1234.

Stomach

Epidemiology and Pathology

Atsuko Kasajima, Günter Klöppel & Stefano La Rosa

Epidemiology

The incidence of gastric NENs is estimated to be 0.4 cases/100,000 person (Dasari et al. 2017; La Rosa and Vanoli 2014). They represent 4% of all NENs, although regional differences among countries have been described (Das and Dasari 2021). Gastric NETs represent 8% of GEP NETs (Alwan et al. 2020), gastric NECs 15–20% of GEP NECs (Milione et al. 2017), and gastric MiNENs 20% of GEP MiNENs (Milione et al. 2017).

Gastric NETs occur most frequently in the sixth decade (Lawrence et al. 2011; Yao et al. 2008). In the very common subtype 1 (80–90% of cases), women are particularly affected, while subtype 2 (5–7% of cases) shows an equal sex distribution, and subtype 3 (10–15% of cases) a predominance of men. NETs arising in the antral mucosa are much rarer (about 5%) than the NETs of the oxyntic-fundic region (La Rosa et al. 2011).

Both gastric NECs and MiNENs are more frequent in males (male/female ratio of 2:1) with an average age at diagnosis of 65 years (range 41–76 years).

Classification

Gastric NENs are classified according to the 2019 WHO criteria into NET G1, G2, and G3 (Table 1), NEC, and MiNEN (Klimstra et al. 2019; La Rosa et al. 2019). In addition, they should be assigned to other prognostic categories considering clinico-pathologic criteria such as gastrin serum level, morphology of the peritumoral mucosa, and presence or absence of an associated MEN1 syndrome (La Rosa and Vanoli 2014; Rindi et al. 1993) (Table 3). Five types are currently distinguished. Type 1 comprises the histamine-producing ECL-cell NETs that are associated with autoimmune chronic atrophic gastritis and type 2 the ECL-cell NETs associated with MEN1-gastrinomas. In type 3, which is neither associated with autoimmune gastritis nor gastrinoma (La Rosa and Vanoli 2014; Rindi et al. 1993), only a fraction of the tumors is really composed of typical ECL-cells. Therefore, the designation "ECL-cell" has been removed in the last WHO classification (La Rosa et al. 2019). Types 4 and 5 are infrequent. The type 4 ECL-cell NET (La Rosa and Vanoli 2014) occurs in patients with hypergastrinemia, achlorhydria, and parietal cell hyperplasia, but without gastrinoma and MEN1 syndrome (Abraham et al. 2005; Ooi et al. 1995). The type 5 ECL-cell NET occurs in patients with moderate hypergastrinemia without chronic atrophic gastritis or gastrinoma, who had been continuously treated for a long time with proton pump inhibitors (La Rosa and Solcia 2020; Trinh et al. 2020). These five types can be further divided into two prognostically relevant groups according to the patients' gastrin levels (Table 3 and Figure 1), because NET patients with hypergastrinemia have a better outcome than NET patients with normogastrinemia. The NETs that arise in the antrum include rare examples of gastrin-, somatostatin- or serotonin-producing tumors.

Gastric NECs and MiNENs differ in morphology and, especially, in genetics, pathogenesis, response to therapy, and outcome and must therefore clearly be distinguished from NETs (Jesinghaus et al. 2017; La Rosa and Uccella 2021; Uccella and La Rosa 2020).

Pathology and Pathogenesis

Gastric NETs

ECL-cell NETs are usually located in the oxyntic mucosa and composed of well-differentiated cells forming small microlobular and/or trabecular structures (Klöppel and La Rosa 2018). In most of cases, ECL-cell NETs express the somatostatin receptor 2A (SSRT2A) and the vesicular monoamine transporter 2 (VMAT2), as well as histidine decarboxylase. Since the NET subtypes have similar histologic features, they have to be distinguished according to the histopathology of the peritumoral mucosa (Figure 2) and the clinico-pathologic context (La Rosa and Vanoli 2014).

Type 1 ECL-cell NETs are usually multiple and small (<1 cm) tumors arising in an atrophic oxyntic mucosa with chronic inflammation, intestinal and pseudopyloric metaplasia, and linear and micronodular ECL-cell hyperplasia. Most of them are G1 NETs although exceptions have been reported (La Rosa

Table 3 Classification and clinico-pathologic features of gastric ECL-cell NETs.

	%	M:F ratio	Average age (years)	Associated disease	Acid secretion	Peritumoral mucosa	ECL-cell prolife-rations	Grade	Metastasis	5-year survival
Associated with hypergastrinemia										
Type 1	80-90%	1:2.5	64	Autoimmune gastritis	Low or absent	Atrophic gastritis	Yes	-G1 -G2, rare -G3, rare	1-3%	about 100%
Type 2	5-7%	1:1	50	Gastrinoma in MEN1 syndrome	High	Hypertrophic gastropathy	Yes	-G1 -G2, rare	10-30%	60-90%
Type 4	Rare	Unknown	50	Hashimoto thyroiditis	Low or absent	Parietal cell hypertrophy	Yes	Unknown	Unknown	Unknown
Type 5^	unknown	1.7:1	60	PPI-treated dyspeptic disease	Not evaluated	PPI effects	Yes	-G1 -G2 -G3, rare	15-17%	about 100%
Not associated with hypergastrinemia										
Type 3*	10-15%	2.8:1	60	None	Normal	No specific change	No	-G1, rare -G2 -G3, rare	50%	<50%

M: male; F: female; PPI: proton pump inhibitors.
^ patients show moderate hypergastrinemia.
* only a fraction of type 3 NETs are composed of ECL-cells.

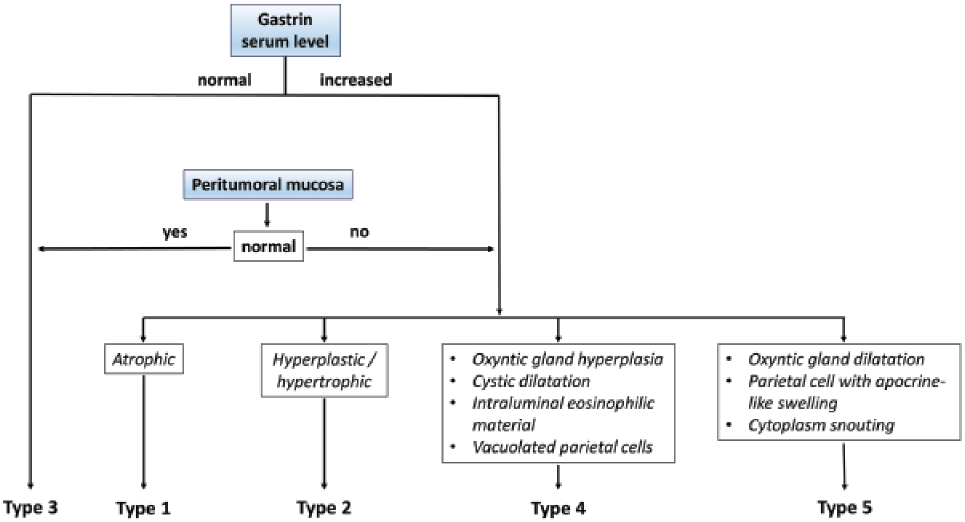
Gastrin serum level
normal
increased
Peritumoral mucosa
yes
normal
no
Atrophic
Hyperplastic / hypertrophic
Oxyntic gland hyperplasia
Cystic dilatation
Intraluminal eosinophilic material
Vacuolated parietal cells
Oxyntic gland dilatation
Parietal cell with apocrine-like swelling
Cytoplasm snouting
Type 3
Type 1
Type 2
Type 4
Type 5

Figure 1 Practical algorithm to diagnose gastric neuroendocrine tumors arising in the oxyntic mucosa. (Reprinted with permission from the article: La Rosa S, Solcia E. New insights into the classification of gastric neuroendocrine tumors, expanding the spectrum of ECL-cell tumors related to hypergastrinaemia. Histopathology 77:862–864, 2020).

et al. 2011), are limited to mucosa or submucosa, and lack any necrosis (Vanoli et al. 2018).

The development of type 1 ECL-cell NETs as well as type 2, 4, and 5 (Sundaresan et al. 2017) is linked to a long-standing hypergastrinemia. However, hypergastrinemia alone seems not to be sufficient for tumor development. In type 1 ECL-cell NETs, gastrin stimulation seems to cooperate with TGF-α and bFGF actions (Bordi 2014). The fact that loss of heterozygosity for *MEN1* gene locus and/or *MEN1* mutations have also been identified in 17–73% of type 1 ECL-cell NETs (Bordi 2014), and the recent identification of a familial cluster bearing mutation of the *ATP4A* proton pump gene (Calvete et al. 2015) further support the notion that genetic,

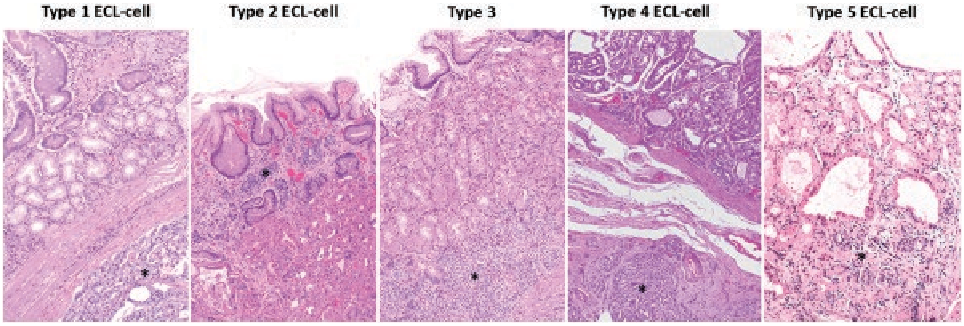

Figure 2 Different type of gastric NETs (asterisks) arising in the oxyntic mucosa. Since they show overlapping morphological features, the morphological aspect of the peritumoral mucosa is an important diagnostic criterion. In type 1 ECL-cell NETs the mucosa is atrophic showing intestinal and pseudopyloric metaplasia. In type 2 ECL-cell NETs the mucosa is hypertrophic-hypersecretory, while in Type 3 NETs the mucosa is normal. Peritumoral mucosa observed in Type 4 ECL-cell NETs shows dilated oxyntic glands containing inspissated secretory material with parietal cells presenting abundant eosinophilic cytoplasm. In Type 5 ECL-cell NETs peritumoral mucosa shows dilation of oxyntic glands in which parietal cells present apocrine-like swelling. (The figure regarding type 4 ECL-cell NET is reprinted with permission from the book chapter: La Rosa S, Uccella S, Rindi G. Neuroendocrine neoplasms of the gut. In: Asa SL, La Rosa S, Mete O. The spectrum of neuroendocrine neoplasia: a practical approach to diagnosis, classification, and therapy. Springer Cam, 2021).

epigenetic, and predisposing genetic factors are likely to be involved in the development of ECL-cell NETs.

Type 2 ECL-cell NETs are multiple and below <2 cm in size arising in a hypertrophic-hypersecretory oxyntic mucosa that shows linear and micronodular ECL-cell proliferations. Most cases are G1 NETs confined to mucosa-submucosa, but G2 cases infiltrating the gastric wall have been described.

Only MEN1-patients with (usually duodenal) gastrinomas develop ECL-cell NETs, while patients with sporadic gastrinomas do not, which indicates that the *MEN1* gene abnormalities are essential for type 2 ECL-cell tumorigenesis.

Type 3 NETs are solitary and generally large (>2 cm) tumors deeply infiltrating the gastric wall. They arise in a normal mucosa without ECL-cell hyperplasia. Most cases are G1 or G2, but G3 NETs have also been described (La Rosa et al. 2011; Vanoli et al. 2018). The pathogenesis of type 3 ECL-cell NETs is not well known, but loss of heterozygosity for *MEN1* gene locus and/or *MEN1* mutations have been identified in 25–50% of type 3 NETs (Bordi 2014). When distinguishing a G3 NET from a NEC, the absence of a p53 overexpression or total loss (corresponding to *TP53* wild type status) and/or Rb1 loss is helpful (Kasajima et al. 2022).

Type 4 ECL-cell NETs are small and multiple tumors arising in a mucosa showing dilated oxyntic glands with parietal cells presenting vacuolated abundant eosinophilic cytoplasm with apical projections into the glandular lumens. The gland lumens contain inspissated secretory material (Abraham et al. 2005; Rindi et al. 1993). Molecular mechanisms involved in the pathogenesis of type 4 ECL-cells NETs are not known so far.

Type 5 ECL-cell NETs present as solitary and small tumors usually confined to mucosa or submucosa. Most tumors are G1 or G2, but rare G3 NETs have been described. The peritumoral mucosa shows PPI effects including dilation of oxyntic glands in which parietal cells show apocrine-like swelling and cytoplasmic snouts. ECL-cell hyperplasia has been observed in about 30% of cases (Trinh et al. 2020). Molecular mechanisms involved in the pathogenesis of type 5 ECL-cells NETs are not known so far.

Gastric NECs and MiNENs

Gastric NECs and MiNENs can occur anywhere in the stomach and present as large, polypoid, ulcerating, or stenotic lesions resembling gastric adenocarcinoma. MiNENs are composed of two morphologically recognizable components, each representing at least 30% of the tumor cell population, although this cutoff has been arbitrarily defined and is now matter of debate (La Rosa and Uccella 2021; Uccella and La Rosa 2020). The neuroendocrine component is often a NEC and only rarely a NET (Klimstra et al. 2019). The non-neuroendocrine component is histologically and immunohistochemically that of a gastric adenocarcinoma (Rindi et al. 2022). Gastric NECs have a high mutational burden characterized by multiple alterations involving *TP53*, *RB1*, *PIK3CA*, *KRAS*, *FHIT*, *DCC*, and *SMAD4* (Makuuchi et al. 2017). Available data on gastric MiNENs indicate the monoclonal origin of the two tumor components and molecular similarities with NECs (Scardoni et al. 2014; Volante et al. 2015).

Prognosis

The prognosis of patients with gastric NETs associated with hypergastrinemia is better than that of patients with normogastrinemia (Table 3). However, among the former NETs some subtype-specific differences are observed. Patients with type 1 ECL-cell NETs have an excellent prognosis with a 10-year survival rate of more than 90%, whereby G1 and G2 cases do not differ significantly from each other in their outcome, suggesting that tumor grade may not be the most important prognostic predictor in this specific subgroup. Conversely, the risk for lymph node metastasis is mainly correlated with tumor size and deep wall invasion (Panzuto et al. 2019; Vanoli et al. 2018) and, for this reason, an accurate endoscopic evaluation of the wall infiltration plays a crucial role in determining the best therapeutic approach rather than the simple evaluation of tumor grade.

Type 2 NETs show lymph node and distant metastases in 30% and 10% of patients, respectively, and the 10-year survival rate is 60–90% (La Rosa and Vanoli 2014).

Due to their extreme rarity, the prognosis of patients with type 4 ECL-cell NETs is not known, although lymph node metastases have been described (Abraham et al. 2005).

Patients with type 5 ECL-cell NETs develop lymph node metastases in about 15% of cases, but show an excellent prognosis, with a 10-year survival rate close to 100% (Trinh et al. 2020).

In contrast, type 3 gastric NETs are aggressive tumors, presenting metastases in about 50% of cases and a 10-year disease-specific survival <50% (La Rosa et al. 2011; Vanoli et al. 2018). In this specific subtype, tumor grade is associated with prognosis (Vanoli et al. 2018).

The rare antral gastrin- and somatostatin-producing NETs are indolent and associated with an excellent prognosis, even in presence of deep wall invasion or lymph node metastasis (La Rosa and Vanoli 2014).

Gastric NECs and MiNENs are aggressive carcinomas associated with a dismal prognosis and a mean survival time of few months. The Ki67 proliferative index, using the cut-off of 55%, is a prognostic factor in NECs, but also in MiNENs, where it needs to be evaluated in the NEC component (La Rosa 2021; Milione et al. 2018, 2017).

Clinical Presentation and Diagnosis

Matthias Schott

Type 1 tumors represent 75–80% of all gastric NENs and, as they involve only patients with atrophic body gastritis (2.4% of patients with atrophy at time of first diagnosis), occur mostly in women and are rarely responsible for symptoms. In fact, they usually are nonfunctioning tumors, typically found during upper-GI endoscopy performed for dyspepsia or for macrocytic or iron deficiency anemia. This condition is associated with slow gastric emptying (explaining dyspepsia) and progressive reduction of acid output, thus impairing iron and vitamin B12 absorption. They present frequently as polyps in the fundic mucosa but can be also detected only at biopsies (previously called microcarcinoids, 22.2%). Type 2 tumors are exclusively seen in multiple endocrine neoplasia type 1 (MEN-1) patients, occurring in 23–29% of such cases (as compared with 1–3% in sporadic gastrinomas), so that genetic testing should be applied in young patients affected by these tumors. They appear as small (diameter 1–2 cm) polyps and may involve the entire fundic mucosa. They are generally asymptomatic. Type 3 tumors may be discovered incidentally, but are often responsible for pain, weight loss, and iron deficiency anemia. Atypical carcinoid syndrome due to histamine production is extremely rare (Gluckman and Metz 2019).

Diagnostic Imaging

Clarisse Dromain & Nicolas Villard

Multiphasic CT that includes the arterial phase and the portal venous phase is the first-line imaging modality.

Imaging features of gastric NENs are depending on the type of gastric NEN. Type 1 (associated with chronic atrophic gastritis) and type 2 (associated with hypergastrinemia) usually appear on CT images as very small (<1 cm) multifocal hypervascular masses located in the fundus or the body of the stomach (Ganeshan et al. 2013). Because of the hypergastrinemia, present in type II, a marked gastric wall thickening may also be present. Type 3 usually present as large hypervascular solid masses.

Duodenum

Epidemiology and Pathology

Atsuko Kasajima, Günter Klöppel & Stefano La Rosa

Epidemiology

The relative frequency of duodenal NETs under all GEP NETs is 2–4%. Their incidence has steadily increased in the past 30 years (Klöppel 2011; Yao et al. 2008). They occur mainly in the sixth decade of life with a similar distribution of male and female patients (Klöppel 2011; Milione et al. 2018).

Classification

Duodenal NENs are classified according to the 2019 WHO criteria into NET G1, G2, and G3 (Table 1), NECs, and MiNENs (Klimstra et al. 2019). Duodenal NETs can be subdivided into three groups based on their histologic, hormonal, and genetic features (Vanoli et al. 2017). I) nonfunctioning NETs without special histologic patterns and immunoreactive for gastrin, somatostatin, and/or serotonin; II) nonfunctioning ampullary NETs with special glandular features and somatostatin immunoreactivity possibly associated with neurofibromatosis type 1 (NF1), or NETs with special gangliocytic and paraganglioma-like features, renamed “composite gangliocytoma/neuroma and neuroendocrine tumor (CoGNET)” in the 2022 WHO classification of neuroendocrine tumors (Rindi et al. 2022); and finally III) functioning NETs with gastrin immunoreactivity associated with Zollinger-Ellison syndrome (ZES) in patients with or without MEN1 syndrome. Most common are small nonfunctioning gastrin-producing NETs followed by somatostatin-producing NETs with glandular features.

Pathology

Nonfunctioning NETs without Special Histologic Patterns

These duodenal NENs are usually well differentiated, smaller than 2 cm, limited to the mucosa-submucosa, localized in the proximal duodenum, and not associated with an inherited syndrome. Most of these tumors produce gastrin (Figure 3 A–B), followed by somatostatin and serotonin, with multihormonality being common. They are positive for SSRT2A and ISLET-1.

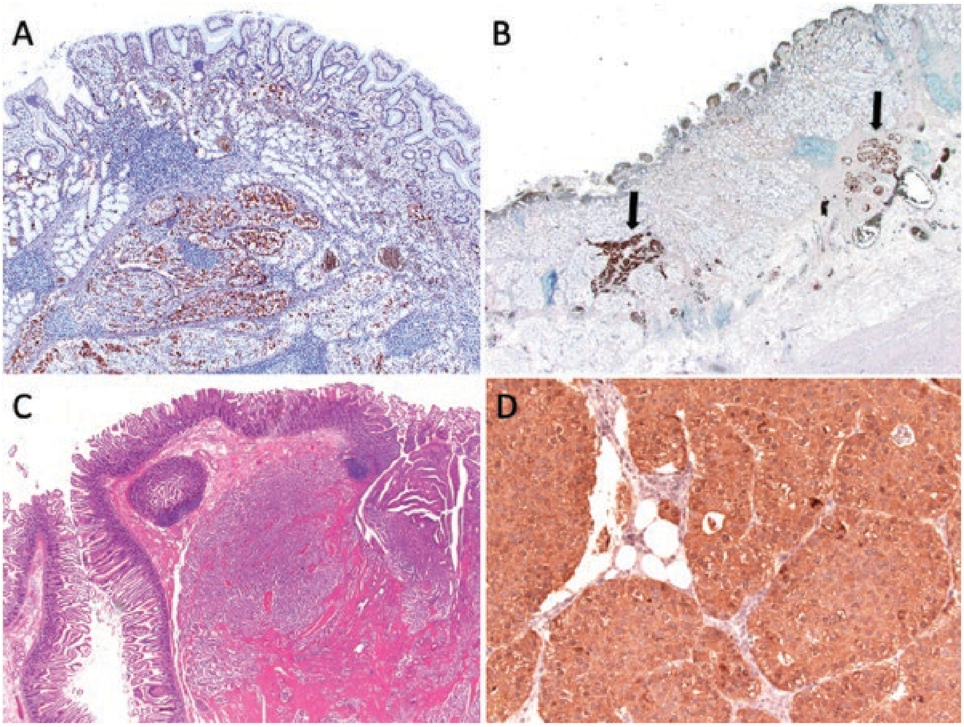

Figure 3 Histological and immunohistochemical images of duodenal neuroendocrine tumors (NETs). **A**: Immunohistochemical gastrin expression in a nonfunctioning duodenal NET. **B** Multiple gastrinomas (arrows) with immunohistochemical gastrin expression in a MEN1 patient. **C**: Histological image of a somatostatin-producing ampullary NET. **D** Immunohistochemical somatostatin expression in ampullary NET.

Lymph node and distant metastases are rare (5–10% of the cases) (Delle Fave et al. 2016; Donow et al. 1991; Rosentraeger et al. 2016; Vanoli et al. 2017).

Nonfunctioning NETs with Special Histologic Patterns

Somatostatin-producing NETs with conspicuous glandular-solid and trabecular structures, often containing psammoma bodies, occur predominantly in the ampullary and periampullary region (Figure 3 C–D) (Garbrecht et al. 2008; Vanoli et al. 2017). When they involve the muscular wall, they have a size of 2 cm or more and an increased proliferation rate, the metastatic risk is over 50% (Vanoli et al. 2017). However, smaller tumors may also metastasize to the paraduodenal lymph nodes. Approximately 10–30% of the somatostatin-producing tumors are associated with NF1 (Dayal et al. 1986; Garbrecht et al. 2008; Vanoli et al. 2017), occasionally combined with a gastrointestinal stroma tumor (GIST). A full somatostatinoma syndrome (diabetes mellitus, diarrhea, steatorrhea, hypo- or achlorhydria, anemia, and gallstones) has not been described so far in association with duodenal somatostatin-producing NETs (Nesi et al. 2008; Vanoli et al. 2017) and its existence has therefore been questioned (Garbrecht et al. 2008).

Composite gangliocytoma/neuroma and neuroendocrine tumor (CoGNET) (traditionally called gangliocytic paraganglioma) are characterized by their triphasic cellular differentiation and are composed of neuroendocrine cells (positive for somatostatin and/or pancreatic polypeptide and ISL1), spindle-shaped Schwann-like cells, and ganglion cells (positive for S-100 and synaptophysin). They usually occur in the periampullary region and follow a benign course. However, occasional, large tumors (size > 2 cm) may spread to local lymph nodes (Garbrecht et al. 2008; Vanoli et al. 2017).

Functioning NETs

Less than 10% of sporadic (non-inherited) duodenal NETs that produce gastrin are functioning and associated with ZES (Rosentraeger et al. 2016) and are called gastrinomas. In 20–35% of cases gastrinomas arise in the setting of MEN1 syndrome (Rosentraeger et al. 2016). The MEN1-associated gastrinomas have, in addition to the *MEN1*-germ line mutation, an allelic loss of 11q13, which is also found in 46% of sporadic gastrinomas. An important histologic difference between sporadic and MEN1-associated gastrinomas is that the latter are multicentric (Figure 3B), show precursor lesions, and metastasize to lymph nodes more often than the sporadic ones (Anlauf et al. 2006; Pipeleers-Marichal et al. 1990; Vanoli et al. 2017). Both gastrinoma types share a low proliferative activity (Ki67 < 2%), a trabecular growth pattern with some solid or pseudoglandular structures, and often produce large lymph node metastases, the size of which usually exceeds that of the primary (Anlauf et al. 2006, 2007; Rosentraeger et al. 2016). SSTR2A labels cell membranes in more than 90% of gastrinomas (Rosentraeger et al. 2016). Serotonin-producing NETs causing a carcinoid syndrome are unusual in the duodenum.

NECs and MiNENs

These neoplasms are very rare and, in contrast to NETs, contain none of the usual hormones and display aberrant p53 and Rb1 expression. Both occur primarily in or close to the ampullary region. Histologically, NECs are often of the large cell type, and become a MiNEN when mixed with an adenocarcinoma. They present in advanced stages, i.e., with lymph node, liver, and other remote metastases (Garbrecht et al. 2008; Yang et al. 2021; Zamboni et al. 1990).

Prognosis

The 10-year survival rate of somatostatin-producing ampullary NETs is 71% and those associated with size < 2 cm have a better prognosis (Garbrecht et al. 2008). The 10-year survival rate of patients with duodenal gastrinomas is worse than that of nonfunctioning duodenal gastrin-producing NETs, but better than that of patients with pancreatic gastrinomas, probably because metastases to the liver are more frequent in pancreatic than duodenal gastrinomas and the local lymph node metastases seem to have little influence on survival (Garbrecht et al. 2008; Jensen et al. 2006).

NECs and MiNENs are very rare. While NECs and MiNENs are prognostically unfavorable, metastatic behavior in NETs is correlated to size (>1 cm), grade (2 and 3), and invasive growth beyond submucosa (Klimstra et al. 2019).

Clinical Presentation and Diagnosis

Matthias Schott

Small nonfunctioning duodenal NETs are detected incidentally; larger tumors can lead to intestinal obstruction or jaundice, depending on the localization. Gastrinoma represents the most common type of functional duodenal NETs and is discussed in detail in the following section.

Gastrinoma

Symptoms and Clinical Signs

Most of the symptoms in patients with gastrinomas are associated with gastric acid hypersecretion. The latter can lead to the development of peptic ulcer, erosive esophagitis, and chronic diarrhea. Symptoms associated with peptic ulcers and their complications (bleeding, perforation, pyloric stenosis) are the most common presenting clinical features in patients with gastrinoma (80%). Peptic ulcers in these patients are often multiple, located in unusual anatomic sites, and resistant to treatment. They are less associated to *Helicobacter pylori* infection compared to idiopathic peptic ulcers (24–48% vs. > 90%, respectively) and are not associated with nonsteroidal anti-inflammatory drugs (NSAID). Erosive esophagitis, causing heartburn and potentially dysphagia, occurs in 50–60% of these patients. Finally, chronic diarrhea is a result of inactivation of pancreatic enzymes (especially lipases), and damage of the intestinal mucosa, due to acid hypersecretion. Gastrinoma-related diarrhea is usually watery, may be associated with malabsorption, and is the only diarrhea that responds dramatically to proton pump inhibitors (PPIs). It occurs in 40–70% of patients with gastrinoma and may be the only symptom in 20% of them (Norton et al. 2018) (Table 4).

Diagnosis

The biochemical confirmation, following clinical suspicion, of a gastrinoma requires a significant elevation of fasting serum gastrin in combination with hyperchlorhydria. The presence of the latter is very important, as hypergastrinemia alone can be a result of chronic hyperchlorhydria/achlorhydria, which is associated with chronic fundus atrophic gastritis, chronic PPI use, as well as vagotomy.

The diagnostic criteria for ZES are as follows: basal acid output (BAO) ≥ 15 mmol/h is suggestive of ZES diagnosis but can overlap with other situations. A threshold value with 100% specificity is obtained only for BAO ≥ 38 mmol/h (Jaïs and Mignon 1995). Elevated fasting serum gastrin is suggestive of ZES, but can be observed in other conditions, like *H. pylori* infection, antral G-cell hyperplasia/hyperfunction, atrophic gastritis, or use of PPIs. Very high fasting serum gastrin levels >100-fold normal (5–9% of ZES patients) are specific of ZES. Normal fasting serum gastrin values have been reported in less than 3% of patients with ZES (Berna et al. 2006). Two-thirds of ZES patients have fasting serum gastrin values <10-fold normal, not specific of ZES. In these two latter situations, gastrin provocative tests are needed to establish the diagnosis. A secretin infusion (2 U/kg intravenously in 2 min) induces a marked increase in both serum gastrin and acid output (≥18 mmol/h) in 90% of ZES patients (Jaïs and Mignon 1995). An increase of serum gastrin >200 pg/mL is diagnostic of ZES (Campana et al. 2005). Recently, a large prospective study proposed new diagnostic criteria (Berna et al. 2006). An increase from fasting gastrin to post-secretin gastrin ≥120 pg/mL has the highest

Table 4 Clinical features of gastrinomas.

Clinical feature	% of patients
Peptic ulcers resistant to treatment, multiple, located in unusual anatomic sites, less associated with H. pylori, and not associated with nonsteroidals	80
Erosive esophagitis causing heartburn and potentially dysphagia, resistant to treatment	50
Diarrhea responding to proton pump inhibitors	40–70
The above features in combination with other endocrinopathies	20
The above features in combination with family history of neuroendocrine tumors	25

sensitivity (94%) and specificity (100%) for diagnosis. The authors suggest that secretin stimulation should be used as the first-line provocative test because of its greater sensitivity and simplicity and lack of side effects. The calcium test should be considered in patients with a strong clinical suspicion of ZES but a negative secretin test. There is agreement in the literature that calcium and meal tests are less useful than secretin for detecting ZES (Norton et al. 2018; Rossi et al. 2021).

Diagnostic Imaging

Clarisse Dromain & Nicolas Villard

Multiphasic CT that includes the arterial phase and the portal venous phase is the first-line imaging modality. Thin sectioning and the use of a negative oral contrast agent are mandatory for the detection of small primary tumor in the duodenum that may not otherwise be seen.

NENs of the duodenum are most often small (mean 1.28 cm), multifocal and preferentially located in the first and the second part of the duodenum. Association with pancreatic NENs is frequent in case of G-cell duodenal gastrinoma associated with MEN-1. On CT or T1W MR images, they present as intraluminal polyps or mural masses showing intense enhancement during the arterial phase with an increase of enhancement on portal phase images. Less often, some tumors present as circumferential wall thickening (Heymann et al. 2004). If a primary tumor is not seen in the duodenum, adjacent enhancing lymphadenopathy, present in 46% of cases, can be a clue to the presence of a duodenal NET (Tsai et al. 2015).

D-cell duodenal somatostatin-secreting tumor usually manifests as a periampullary tumor that may obstruct the common bile duct with upstream dilatation (Ganeshan et al. 2013).

Surgical Treatment

Levent Dizdar & Wolfram Trudo Knoefel

Gastric NENs

Surgical treatment of gastric NENs depends crucially on the tumor type which is important for the prediction of malignant potential and prognosis. In addition, tumor size and the presence of lymph node or distant metastases play an important role in determining the indication for surgical intervention. The only chance for cure is complete resection of the tumor.

Type 1 gastric NETs should be treated by surgical resection if the tumor is larger than 2 cm, if the muscle wall is infiltrated, if lymph node or distant metastases are detectable, or the resection margin is positive after endoscopic resection (endoscopic mucosal resection/endoscopic submucosal dissection) (Basuroy et al. 2014; Partelli et al. 2014). Little evidence exists regarding the extent of resection. In the absence of lymph node metastases, organ-preserving resections such as wedge resection or 2/3 gastrectomy without systematic lymphadenectomy appear to be sufficient. If lymph node metastases are present, partial, subtotal, or total gastrectomy with D2 lymphadenectomy should be performed. Antrectomy is a surgical treatment option for patients with multifocal, invasive, or recurrent type 1 gastric NETs. Resection of the antrum eliminates the G-cell-mediated hypergastrinemia, resulting in regression of gastric NENs in more than 90% of the cases (Ozao-Choy et al. 2010; Jenny et al. 2016).

Surgical resection for ***type 2 gastric NETs*** is indicated in analogy to type 1 gastric NETs for invasive, metastatic, or endoscopically incompletely resected tumors. Antrectomy is not indicated for type II NETs because the hypergastrinaemia does not originate from the gastric antrum. Instead, the gastrinoma causing the hypegastrinemia should be identified and resected. For this purpose, surgical removal of duodenal gastrinomas (by duodenotomy with lymphadenectomy or partial duodenopancreatectomy) may be required.

Type 3 NET and NECs are characterized by an aggressive course with early metastasis. Therefore, depending on tumor localization, a subtotal or total gastrectomy with D2 lymphadenectomy is indicated. An exception to this approach could potentially involve small (<2 cm), G1/G2 type 3 gastric NENs, which are confined to the submucosa and do not show lymphovascular invasion. Endoscopic resection could be a reasonable alternative to surgery in this selected subgroup (Kwon et al. 2013). In patients with metastatic, poorly differentiated gastric NECs, surgery is usually not recommended, and systemic therapy should be initiated (Garcia-Carbonero et al. 2016).

Duodenal NENs

Basically, all duodenal NENs should be removed, unless unresectable metastases or severe comorbidities are present. Procedures used in the resection of duodenal NENs range from endoscopic resections to transduodenal local excisions to aggressive resection procedures such as partial pancreatoduodenectomy (PPD) (Delle Fave et al. 2012; Jensen et al. 2012). The choice of the resection procedure is primarily based on the size, location, histologic grade and stage, as well as hormonal activity of the tumor. Small (≤1 cm) well-differentiated duodenal NETs without metastases or hormonal activity can be resected with endoscopic techniques if they are not located in the periampullary region (Delle Fave et al. 2012). For tumors localized in the periampullary region, local surgical resection with lymphadenectomy or picking is recommended in current guidelines, even for small tumors (≤1 cm). For NENs of the ampulla, surgical resection by PPD is commonly recommended, as tumor size in this location appears to be less closely associated with the malignant potential of the neoplasia (Delle Fave et al. 2012; Randle et al. 2014). However, some studies indicate that for small (<2 cm), well-differentiated (G1) ampullary NETs, endoscopic papillectomy may represent a curative therapy if no metastases are detectable (De Palma et al. 2010; Odabasi et al. 2013). Treatment of duodenal NENs 1–2 cm in size is controversial, with some data suggesting that endoscopic resection is reasonable if there is no evidence of lymph node metastasis (Kachare et al. 2014), while others recommend surgery for these tumors (Zyromski et al. 2001). According to current evidence, duodenal NENs >

2 cm or tumors of any size with suspected lymph node metastases should undergo surgical resection (Delle Fave et al. 2012). The choice of the type of surgical resection is largely based on the size and localization of the tumor. NENs in the first part of the duodenum can often be removed by local resection, those in the fourth part by distal duodenectomy. NENs in the second and third part of the duodenum, however, usually require a PPD (Delle Fave et al. 2012). Duodenal NETs with potentially resectable liver metastases but without other distant metastases and without comorbidities that limit life expectancy or substantially increase the risk of surgery may be considered for resection (Delle Fave et al. 2012). However, when distant metastatic, poorly differentiated neuroendocrine carcinoma of the duodenum is detected, an absolute contraindication to surgical resection exists (Garcia-Carbonero et al. 2016).

Surgical Treatment of Zollinger-Ellison Syndrome (ZES)/Gastrinoma

The vast majority of gastrinomas are located in the duodenum or pancreas. In 60–90% of patients with both sporadic ZES and MEN1/ZES, a gastrinoma is found in the duodenum. Patients with sporadic gastrinoma, with potentially resectable disease and without serious comorbidities, should undergo routine surgical exploration for cure as lymph node metastases are present in at least half of all cases and surgery is known to decrease the rate of hepatic metastases and to prolong disease-related survival (Fraker et al. 1994; Norton and Jensen 2004). The extent of resection depends on the size and location of the gastrinoma, and ranges from local excision to PPD. However, systematic lymphadenectomy (hepatoduodenal ligament, hepatic artery, and retropancreatic) as well as an intraoperative sonography of the liver should always be routinely performed given the high rate of metastases (Bartsch et al. 2012). Up to 30% of sporadic gastrinomas cannot be precisely localized preoperatively. In this situation, the indication for surgical exploration should still be made after multidisciplinary discussion, since in up to 90% of these cases the primary tumor can be detected intraoperatively by the surgeon (Deutsche Gesellschaft fur Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten et al. 2018; Jensen et al. 2012; Morrow and Norton 2009). In the case of negative preoperative imaging, surgical exploration should include complete exposure of the pancreas with bidigital palpation and intraoperative ultrasound as well as a duodenotomy with duodenal transillumination, if necessary, and a routine lymphadenectomy in the gastrinoma triangle (Deutsche Gesellschaft fur Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Morrow and Norton 2009). Laparoscopic resection of gastrinomas is generally not recommended as the primary tumor is often not detectable during preoperative examinations and difficult to identify intraoperatively (Deutsche Gesellschaft fur Gastroenterologie V-uS et al. 2018; Jensen et al. 2012).

MEN1-associated gastrinomas are usually multifocal, involving the duodenum and only rarely the pancreas. Surgical treatment of MEN1 gastrinomas is associated with a recurrence rate of >90% if PPD is not performed (Jensen et al. 2012; Norton and Jensen 2004). Furthermore, patients with only small pancreatic tumors (<2 cm) have an excellent life expectancy. Therefore, routine surgical exploration in patients with MEN1-associated gastrinomas is controversial (Jensen et al. 2008, 2012; Norton and Jensen 2004). It is generally recommended that surgery should be limited to MEN1 pancreatic tumors larger than 2 cm to prevent metastasis (Deutsche Gesellschaft fur Gastroenterologie V-uS et al. 2018; Jensen et al. 2008, 2012; Norton and Jensen 2004). However, it should be discussed with the patient that surgery at the time of biochemical evidence of the disease offers the greatest chance of biochemical cure. PPD is associated with the highest long-term biochemical cure rate (80–90%) compared with so-called non-PPD resections (PPD 90% vs. non-PPD 30%). Nevertheless, non-PPD resections, including duodenotomy with excision of gastrinomas of the duodenal wall with or without distal pancreatic resection, are associated with very good long-term survival. Consequently, the role of PPD resection in patients with MEN1-associated gastrinomas is currently unclear (Deutsche Gesellschaft fur Gastroenterologie V-uS et al. 2018; Jensen et al. 2012).

References

Abraham, S.C., Carney, J.A., Ooi, A. et al. (2005). Achlorhydria, parietal cell hyperplasia, and multiple gastric carcinoids: a new disorder. *Am J Surg Pathol* 29: 969–975.

Alwan, H., La Rosa, S., Kopp, A.P. et al. (2020). Incidence trends of lung and gastroenteropancreatic neuroendocrine neoplasms in Switzerland. *Cancer Med* 9 (24): 9454–9461.

Anlauf, M., Garbrecht, N., Henopp, T. et al. (2006). Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. *World J Gastroenterol* 12 (34): 5440–5446.

Anlauf, M., Perren, A., and Klöppel, G. (2007). Endocrine precursor lesions and microadenomas of the duodenum and pancreas with and without MEN1: criteria, molecular concepts and clinical significance. *Pathobiology* 74 (5): 279–284.

Bartsch, D.K., Waldmann, J., Fendrich, V. et al. (2012). Impact of lymphadenectomy on survival after surgery for sporadic gastrinoma. *Br J Surg* 99 (9): 1234–1240.

Basuroy, R., Srirajaskanthan, R., Prachalias, A. et al. (2014). Review article: the investigation and management of gastric neuroendocrine tumours. *Aliment Pharmacol Ther* 39 (10): 1071–1084.

Berna, M.J., Hoffmann, K.M., Serrano, J. et al. (2006). Serum gastrin in Zollinger-Ellison syndrome: i. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. *Medicine (Baltimore)* 85 (6): 295–330.

Bordi, C. (2014). Neuroendocrine pathology of the stomach: the Parma contribution. *Endocr Pathol* 25 (2): 171–180.

Calvete, O., Reyes, J., Zuniga, S. et al. (2015). Exome sequencing identifies *ATP4A* gene as responsible of an atypical familial type I gastric neuroendocrine tumour. *Hum Mol Genet* 24: 2914–2922.

Campana, D., Piscitelli, L., Mazzotta, E. et al. (2005). Zollinger-Ellison syndrome. Diagnosis and therapy. *Minerva Med* 96 (3): 187–206.

Das, S. and Dasari, A. (2021). Epidemiology, incidence, and prevalence of neuroendocrine neoplasms: are there global differences? *Curr Oncol Rep* 14; 23 (4): 43.

Dasari, A., Shen, C., and Halperin, D. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 3: 1335–1342.

Dayal, Y., Tallberg, K.A., Nunnemacher, G. et al. (1986). Duodenal carcinoids in patients with and without neurofibromatosis. A comparative study. *Am J Surg Pathol* 10 (5): 348–357.

De Palma, G.D., Masone, S., Siciliano, S. et al. (2010). Endocrine carcinoma of the major papilla: report of two cases and review of the literature. *Surg Oncol* 19 (4): 235–242.

Delle Fave, G., Kwekkeboom, D.J., Van Cutsem, E. et al. (2012). ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. *Neuroendocrinology* 95 (2): 74–87.

Delle Fave, G., O'Toole, D., Sundin, A. et al. (2016). ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. *Neuroendocrinology* 103 (2): 119–124.

Deutsche Gesellschaft fur Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS), Netzwerk Neuroendokrine Tumoren e V, Bundesorganisation Selbsthilfe NeuroEndokrine Tumoren e V, Deutsche Gesellschaft fur Hamatologie und Medizinische Onkologie e.V uAIOdDKeV, Deutsche Gesellschaft fur Allgemein- und Viszeralchirurgie e.V, Deutsche Gesellschaft für C et al. (2018). Practice guideline neuroendocrine tumors - AWMF-Reg. 021-27. *Z Gastroenterol* 56 (6): 583–681.

Donow, C., Pipeleers-Marichal, M., Schroder, S. et al. (1991). Surgical pathology of gastrinoma. Site, size, multicentricity, association with multiple endocrine neoplasia type 1, and malignancy. *Cancer* 68 (6): 1329–1334.

Fraker, D.L., Norton, J.A., Alexander, H.R. et al. (1994). Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. *Ann Surg* 220 (3): 320–328; discussion 8-30.

Ganeshan, D., Bhosale, P., Yang, T., and Kundra, V. (2013). Imaging features of carcinoid tumors of the gastrointestinal tract. *AJR Am J Roentgenol* 201 (4): 773–786.

Garbrecht, N., Anlauf, M., Schmitt, A. et al. (2008). Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. *Endocr Relat Cancer* 15 (1): 229–241.

Garcia-Carbonero, R., Sorbye, H., Baudin, E. et al. (2016). ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology* 103 (2): 186–194.

Gluckman, C.R. and Metz, D.C. (2019). Gastric neuroendocrine tumors (Carcinoids). *Curr Gastroenterol Rep* 21 (4): 13.

Heymann, M.F., Hamy, A., Triau, S. et al. (2004). Endocrine tumors of the duodenum. A study of 55 cases relative to clinicopathological features and hormone content. *Hepatogastroenterology* 51 (59): 1367–1371.

Jaïs, P. and Mignon, M. (1995). Normal serum gastrin concentration in gastrinoma. *Lancet* 346 (8987): 1421–1422.

Jenny, H.E., Ogando, P.A., Fujitani, K. et al. (2016). Laparoscopic antrectomy: a safe and definitive treatment in managing type 1 gastric carcinoids. *Am J Surg* 211 (4): 778–782.

Jensen, R.T., Berna, M.J., Bingham, D.B., and Norton, J.A. (2008). Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 113 (7 Suppl): 1807–1843.

Jensen, R.T., Cadiot, G., Brandi, M.L. et al. (2012). ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 95 (2): 98–119.

Jensen, R.T., Niederle, B., Mitry, E. et al. (2006). Gastrinoma (duodenal and pancreatic). *Neuroendocrinology* 84 (3): 173–182.

Jesinghaus, M., Konukiewitz, B., Keller, G. et al. (2017). Colorectal mixed adenoneuroendocrine carcinomas and neuroendocrine carcinomas are genetically closely related to colorectal adenocarcinomas. *Mod Pathol* 30: 610–619.

Kachare, S.D., Liner, K.R., Vohra, N.A. et al. (2014). A modified duodenal neuroendocrine tumor staging schema better defines the risk of lymph node metastasis and disease-free survival. *Am Surg* 80 (8): 821–826.

Kasajima, A., Konukiewitz, B., Schlitter, A.M. et al. (2022). An analysis of 130 neuroendocrine tumors G3 regarding prevalence, origin, metastasis, and diagnostic features. *Virchows Arch* 480 (2): 359–368.

Klimstra, D.S., Klöppel, G., La Rosa, S., and Rindi, G. (2019). Classification of neuroendocrine neoplasms of the digestive system. In: *WHO Classification of Tumours*, 5e (ed. WHO classification of tumours editorial board), 16–19. Digestive system tumours. Lyon: IARC.

Klöppel, G. (2011). Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 18 (Suppl 1): S1–16.

Klöppel, G. and La Rosa, S. (2018). Ki67 labeling index: assessment and prognostic role in gastroenteropancreatic neuroendocrine neoplasms. *Virchows Arch* 472: 341–349.

Kwon, Y.H., Jeon, S.W., Kim, G.H. et al. (2013). Long-term follow up of endoscopic resection for type 3 gastric NET. *World J Gastroenterol* 19 (46): 8703–8708.

La Rosa, S. (2021). Challenges in high-grade neuroendocrine neoplasms and mixed neuroendocrine/non-neuroendocrine neoplasms. *Endocr Pathol* 32 (2): 245–257.

La Rosa, S., Inzani, F., Vanoli, A. et al. (2011). Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. *Hum Pathol* 42 (10): 1373–1384.

La Rosa, S., Rindi, G., Solcia, E., and Tang, L.H. (2019). Gastric neuroendocrine neoplasms. In: *WHO Classification of Tumours*, 5e (ed. WHO classification of tumours editorial board), 104–109. Digestive system tumours. Lyon: IARC.

La Rosa, S. and Solcia, E. (2020). New insights into the classification of gastric neuroendocrine tumors, expanding the spectrum of ECL-cell tumours related to hypergastrinaemia. *Histopathology* 77: 862–864.

La Rosa, S. and Uccella, S. (2021). Classification of neuroendocrine neoplasms: lights and shadows. *Rev Endocr Metab Disord* 22 (3): 527–538.

La Rosa, S. and Vanoli, A. (2014). Gastric neuroendocrine neoplasms and related precursor lesions. *J Clin Pathol* 67 (11): 938–948.

Lawrence, B., Gustafsson, B.I., Chan, A. et al. (2011). The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 40 (1): 1–18.

Makuuchi, R., Terashima, M., Kusuhara, M. et al. (2017). Comprehensive analysis of gene mutation and expression profiles in neuroendocrine carcinomas of the stomach. *Biomed Res* 38 (1): 19–27.

Milione, M., Maisonneuve, P., Pellegrinelli, A. et al. (2018). Ki67 proliferative index of the neuroendocrine component drives MANEC prognosis. *Endocr Relat Cancer* 25 (5): 583–593.

Milione, M., Maisonneuve, P., Spada, F. et al. (2017). The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories. *Neuroendocrinology* 104 (1): 85–93.

Morrow, E.H. and Norton, J.A. (2009). Surgical management of Zollinger-Ellison syndrome; state of the art. *Surg Clin North Am* 89 (5): 1091–1103.

Nesi, G., Marcucci, T., Rubio, C.A. et al. (2008). Somatostatinoma: clinico-pathological features of three cases and literature reviewed. *J Gastroenterol Hepatol* 23 (4): 521–526.

Norton, J.A., Foster, D.S., Ito, T., and Jensen, R.T. (2018). Gastrinomas: medical or surgical treatment. *Endocrinol Metab Clin North Am* 47 (3): 577–601.

Norton, J.A. and Jensen, R.T. (2004). Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann Surg* 240 (5): 757–773.

Odabasi, M., Yildiz, K.M., Cengiz, E. et al. (2013). Treatment of ampullary neuroendocrine tumor by endoscopic snare papillectomy. *Am J Case Rep* 14: 439–443.

Ooi, A., Ota, M., Katsuda, S. et al. (1995). An unusual case of multiple gastric carcinoids associated with diffuse endocrine cell hyperplasia and parietal cell hypertrophy. *Endocr Pathol* 6: 229–237.

Ozao-Choy, J., Buch, K., Strauchen, J.A. et al. (2010). Laparoscopic antrectomy for the treatment of type I gastric carcinoid tumors. *J Surg Res* 162 (1): 22–25.

Panzuto, F., Campana, D., Massironi, S. et al. (2019). Tumour type and size are prognostic factors in gastric neuroendocrine neoplasia: a multicentre retrospective study. *Dig Liver Dis* 51 (10): 1456–1460.

Partelli, S., Maurizi, A., Tamburrino, D. et al. (2014). GEP-NETS update: a review on surgery of gastro-entero-pancreatic neuroendocrine tumors. *Eur J Endocrinol* 171 (4): R153–62.

Pipeleers-Marichal, M., Somers, G., Willems, G. et al. (1990). Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. *N Engl J Med* 322 (11): 723–727.

Randle, R.W., Ahmed, S., Newman, N.A., and Clark, C.J. (2014). Clinical outcomes for neuroendocrine tumors of the duodenum and ampulla of Vater: a population-based study. *J Gastrointest Surg* 18 (2): 354–362.

Rindi, G., Luinetti, O., Cornaggia, M. et al. (1993). Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 104: 994–1006.

Rindi, G., Mete, O., Uccella, S. et al. (2022). Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol* 33 (1): 115–154.

Rosentraeger, M.J., Garbrecht, N., Anlauf, M. et al. (2016). Syndromic versus non-syndromic sporadic gastrin-producing neuroendocrine tumors of the duodenum: comparison of pathological features and biological behavior. *Virchows Arch* 468 (3): 277–287.

Rossi, R.E., Elvevi, A., Citterio, D. et al. (2021). Gastrinoma and Zollinger Ellison syndrome: a roadmap for the management between new and old therapies. *World J Gastroenterol* 27 (35): 5890–5907.

Scardoni, M., Vittoria, E., Volante, M. et al. (2014). Mixed adeno-neuroendocrine carcinomas of the gastrointestinal tract: targeted next-generation sequencing suggests a monoclonal origin of the two components. *Neuroendocrinology* 100 (4): 310–316.

Sundaresan, S., Kang, A.J., and Merchant, J.L. (2017). Pathophysiology of fastric NETs: role of gastrin and menin. *Curr Gastroenterol Rep* 19 (7): 32.

Trinh, V.Q., Shi, C., and Ma, C. (2020). Gastric neuroendocrine tumors from long-term proton pump inhibitor users are indolent tumors with good prognosis. *Histopathology* 77: 865–876.

Tsai, S.D., Kawamoto, S., Wolfgang, C.L. et al. (2015). Duodenal neuroendocrine tumors: retrospective evaluation of CT imaging features and pattern of metastatic disease on dual-phase MDCT with pathologic correlation. *Abdom Imaging* 40 (5): 1121–1130.

Uccella, S. and La Rosa, S. (2020). Looking into digestive mixed neuroendocrine - nonneuroendocrine neoplasms: subtypes, prognosis, and predictive factors. *Histopathology* 77 (5): 700–717.

Vanoli, A., La Rosa, S., Klersy, C. et al. (2017). Four neuroendocrine tumor types and the neuroendocrine carcinoma of the duodenum: analysis of 203 cases. *Neuroendocrinology* 104 (2): 112–125.

Vanoli, A., La Rosa, S., Miceli, E. et al. (2018). Prognostic evaluations tailored to specific gastric neuroendocrine neoplasms: analysis of 200 cases with extended follow-up. *Neuroendocrinology* 107 (2): 114–126.

Volante, M., Monica, V., Birocco, N. et al. (2015). Expression analysis of genes involved in DNA repair or synthesis in mixed neuroendocrine/nonneuroendocrine carcinomas. *Neuroendocrinology* 101 (2): 151–160.

Yang, S., Lu, J., Cai, Y. et al. (2021). Mixed adenoneuroendocrine carcinomas of stomach and ampulla of vater after curative-intent resection: a single center cases series. *BMC Gastroenterol* 21 (1): 329.

Yao, J.C., Hassan, M., Phan, A. et al. (2008). One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26 (18): 3063–3072.

Zamboni, G., Franzin, G., Bonetti, F. et al. (1990). Small-cell neuroendocrine carcinoma of the ampullary region. A clinicopathologic, immunohistochemical, and ultrastructural study of three cases. *Am J Surg Pathol* 14 (8): 703–713.

Zyromski, N.J., Kendrick, M.L., Nagorney, D.M. et al. (2001). Duodenal carcinoid tumors: how aggressive should we be? *J Gastrointest Surg* 5 (6): 588–593.

Pancreas

Epidemiology and Pathology

Irene Esposito, Lena Häberle & Björn Konukiewitz

Epidemiology

Epidemiological studies about pancreatic NENs (PanNENs) mostly refer to the category of well-differentiated NETs, whereas much less data is available regarding NECs due to their rarity and, possibly, to difficulty in classification.

PanNETs represent about 10% of all GEP-NETs according to the SEER data (Lee et al. 2019) and their incidence is increasing in all age groups, with a linear increase in the > 50 age group (Das and Dasari 2021) and an incidence rate of 0.33/100.000 without any relevant sex difference. The median age at diagnosis is 63 years, and the peak incidence is found at the age of 70–75; PanNETs are rare before the age of 35 (Lee et al. 2019). In some geographical areas, PanNETs represent the most frequent GEP-NETs, as for example in some European countries like Portugal and some Asiatic countries, like India and China (Das and Dasari 2021).

PanNET show the lowest 5-years survival rate (37.6%) among GEP-NETs according to the SEER data (Lee et al. 2019). Higher survival rates have been reported in other countries, such as Canada (48.8%) (Hallet et al. 2015) and Norway (43%) (Hauso et al. 2008). The tumor stage and the grading are the most relevant factors associated with prognosis.

PanNECs are exceedingly rare and make-up about 20% of all GEP-NECs according to a SEER database analysis (Dasari et al. 2018). The incidence of GEP-NECs has been increasing steadily in the last 40 years, but it remains <1 case/100.000/year, same holding true for PanNECs. PanNECs are slightly more common in male than in females (56 vs. 44%) and the median age at diagnosis is 67 years. Most cases (75%) have distant metastasis at the time of diagnosis and poor median survival of only 5.7 months. Large cell histology seems to be more common (about 60%) (Basturk et al. 2014).

The recently defined category of G3 NET (see Introduction) has been most probably neglected in the available datasets, so that their frequency can be only inferred from retrospective series. For example, Kasajima et al. reported a frequency of 9% of G3 NETs in a consultation series comprising 1513 NENs from all sites; in 42% of the cases, the G3 NET originated from the pancreas (Kasajima et al. 2022). A single institution series from China, which included 480 Pan-NENs, identified 64 NETs G3 (13%), and 108 NECs (22.5%) (Yang et al. 2020). Altogether, G3-NET seems to represent about one-fourth of all G3 GEP-NENs (Heetfeld et al. 2015; Scoazec et al. 2017), but this figure might be underestimated.

Risk factors for PanNENs include a positive family history for cancer, smoking, alcohol consumption, obesity, and diabetes (Leoncini et al. 2016). In addition, 10–20% of PanNETs are associated with hereditary syndromes (see below, *GEP-NENs and Hereditary Syndromes*).

Pathology – General Considerations

PanNENs are classified in well-differentiated NETs and poorly differentiated NECs based on their morphologic appearance.

PanNETs occur everywhere in the pancreas; they are usually well circumscribed, but they may show a multinodular infiltrative growth, or a cystic appearance. Size at diagnosis usually ranges between 2 and 5 cm; the consistency varies depending on the amount of stroma, the color is reddish to yellowish-brown, necrosis is rare (Figure 4). PanNETs with a size of < 5 mm are designated microtumors and are usually detected incidentally at histological examination (WHO Classifications of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet] 2022).

PanNETs display a wide spectrum of growth patterns, including solid-nested, reticulated-trabecular, gyriform, glandular, and solid-paranganglioma-like (Figure 5). The tumor cells are usually cuboidal to cylindrical with monotonous nuclei displaying the classical "salt and pepper" chromatin appearance; clear-cell and oncocytic variants as well as pleomorphic cells with prominent nucleoli have been described. The stroma is mostly scant and richly vascularized, but it may be abundant and sclerotic; calcifications, sometimes in form of psammoma bodies, may occur (Konukiewitz et al. 2022).

Some morphological patterns are associated with specific hormone-producing entities (see below, *Specific Entities*).

PanNETs are usually diffusely positive for cytokeratins, synaptophysin, INSM1 (Konukiewitz et al. 2022), CD56, and CD57. Chromogranin A is usually positive, but the expression is more frequently focal and shows an apical localization within the cytoplasm. Independently from their functional activity, PanNETs often express specific hormones, the most common being glucagon, somatostatin, and pancreatic polypeptide. In addition, they are positive for the transcription factor ISLET1 and they usually show a strong membranous expression of the somatostatin-receptor 2A (SSTR2A).

Depending on the proliferation rate, as assessed by the Ki-67 staining or on the number of mitoses/2mm^2, PanNETs are graded into G1, G2, or G3 categories, as discussed above (Introduction, Table 1).

PanNECs are usually larger at diagnosis (mean size: 4 cm); they have a whitish color and a fleshy consistency and often display necrosis and hemorrhage. The small-cell subtype consists of solid sheets of cells with scant cytoplasm and round nuclei with inconspicuous nucleoli. Mitoses and apoptosis are common. The more frequent large-cell subtype often displays organoid, nested, or trabecular patterns of growth; the cells have large nuclei with evident nucleoli and a wider, eosinophilic or amphiphilic cytoplasm (Basturk et al. 2014).

PanNECs express cytokeratins, often with a punctuated pattern. Synaptophysin is quite sensitive for the diagnosis of PanNECs, whereas chromogranin A is very specific, but it displays a limited sensitivity. ISLET1 and SSTR2A are usually negative in PanNECs. The Ki-67 proliferation rate of PanNECs usually exceeds 50–60%. Altered expression pattern of p53 or Rb indicates a mutation of the respective gene, and it is useful for the differential diagnosis between highly proliferating NETs (G3-NETs) and NECs (Konukiewitz et al. 2017; Tang et al. 2016).

Pathology – Specific Entities

Nonfunctioning PanNETs account for approximately 70% of all PanNETs. This group comprises a plethora of heterogenous tumors either without or with production of peptide hormones that are not associated with a clinical syndrome linked to the secretion of hormones. Hormone-producing nonfunctioning PanNETs can be characterized by the production of orthotopic (insulin, glucagon, somatostatin, pancreatic polypeptide) or ectopic hormones (gastrin, serotonin, ACTH, among others). The hormones are located in the cytoplasm of the tumor cells and can easily be detected by immunohistochemistry (Konukiewitz et al. 2022). The spectrum of hormone expression ranges from single cells to a strong and diffuse positivity in all tumor cells. Multihormonal tumors are common (Kapran et al. 2006; Konukiewitz et al. 2020). Nonfunctioning PanNETs nearly show the whole spectrum of organoid neuroendocrine

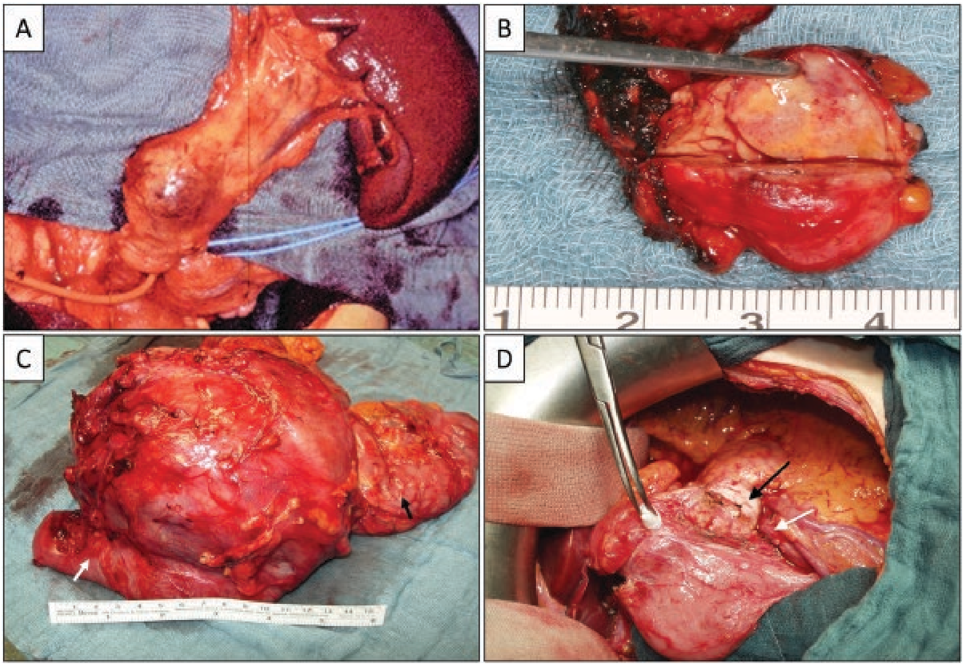

Figure 4 PanNET. **A**: Intraoperative finding of a patient with a glucagonoma involving the pancreatic tail. The spleen as well as the distal pancreas were mobilized before performing the resection. **B**: Surgical specimen of a pancreatic NET after spleen-preserving resection. **C**: Resection specimen of a malignant insulinoma with infiltration of the transverse colon. The black arrow indicates the transverse colon, the white arrow marks the duodenum. **D**: Intraoperative finding of a glucagonoma in the pancreatic corpus. The white arrow indicates the superior mesenteric vein, the black arrow the glucagonoma.

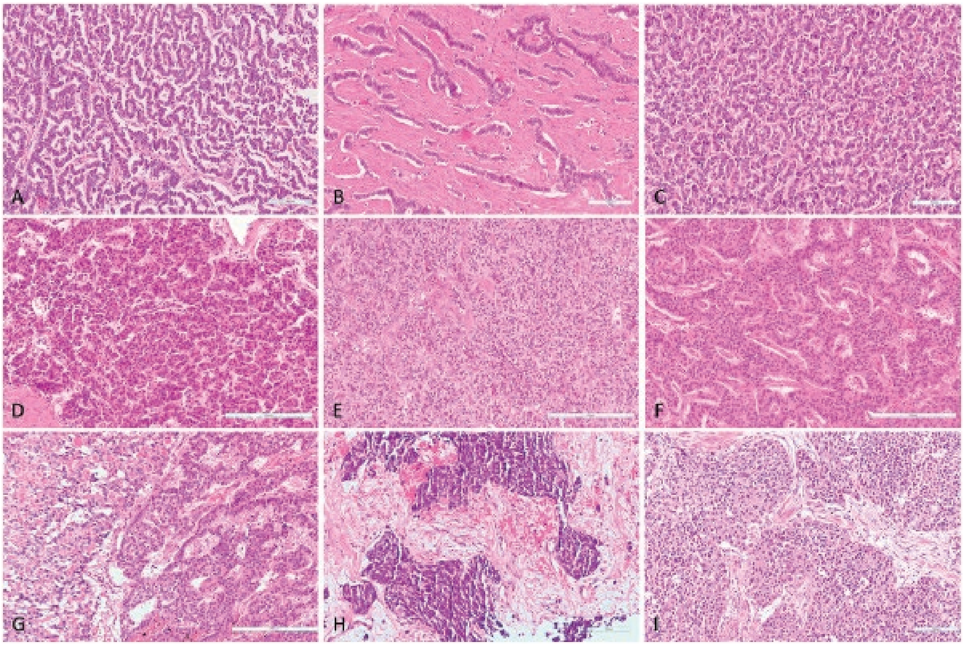

Figure 5 Morphological subtypes of PanNENs. **A**: NET, gyriform pattern; **B**: NET, cord-like pattern; **C** NET, reticulated-trabecular pattern; **D** NET eosinophilic trabecular patter; **E** NET, clear-cell nested-trabecular pattern; **F** NET, glandular pattern; **G** NET, mixed microacinar (left) and gyriform-trabecular pattern; **H** small cell NEC; **I** large cell NEC.

growth patterns, which is in fact very heterogeneous, but can be traced back to solid and trabecular patterns. These two patterns can be furthermore subdivided due to the composition of the tumor's stroma (Konukiewitz et al. 2020). It is more and more recognized that some histological growth patterns are associated with the production of a specific hormone. It has been shown that the trabecular-reticulated and cystic patterns are associated with the production of glucagon (Konukiewitz et al. 2011). PanNETs with a solid paraganglioma-like morphology express somatostatin (Konukiewitz et al. 2020). Tumors with a trabecular-sclerosing pattern often produce serotonin; these tumors are interestingly often located near large ducts (McCall et al. 2012). Solid-nested patterns with amyloid are found in insulin-producing PanNETs, but this special tumor fall into the category of functional PanNETs (see below).

Functioning PanNETs are associated with a paraneoplastic clinical syndrome that is caused by the production and the secretion of a peptide hormone by the tumor. They account for approximately 30% of PanNETs and include mostly insulinoma and gastrinoma, followed by rare functioning PanNETs such as VIPoma, glucagonoma, serotonin-producing tumors with carcinoid syndrome, ACTHoma, and others, exceedingly rare functioning PanNETs (Konukiewitz et al. 2022; WHO Classification of Tumours Editorial Board 2022). Somatostatinomas have also been described, but recent studies could not verify any syndrome linked to the production of somatostatin (Garbrecht et al. 2008; Krejs et al. 1979).

Insulinoma is the most common functioning PanNET and accounts for about 70% of the cases. It can arise in all regions of the pancreas. Most insulinomas are small tumors at time of diagnosis (<2 cm) with a low proliferative index and an excellent prognosis with a 10-year survival rate of nearly 100%. Larger tumors (>2 cm) often metastasize (WHO Classification of Tumours Editorial Board. Digestive system tumours 2019). Insulinoma are strongly insulin-positive; some cases show typical stroma deposits of amyloid. Biological aggressive cases sometimes contain just few insulin-positive tumor cells and can be multihormonal (Konukiewitz et al. 2022). Multiple insulinomas can arise in the context of multiple endocrine neoplasia type 1 or rarely in the context of insulinomatosis (Anlauf et al. 2009, 2007).

Gastrinomas are the second common functioning PanNETs and cause the Zollinger-Ellison syndrome due to the secretion of gastrin. Gastrinomas are mostly sporadic tumors but can occur in the context of MEN1 syndrome. They can arise in all regions of the pancreas (Anlauf et al. 2006a). The prognosis of gastrinoma is not different to that of nonfunctioning PanNETs (WHO Classification of Tumours Editorial Board 2019).

VIPoma, glucagonoma, serotonin-producing tumors with carcinoid syndrome, and ACTH-secreting tumors are rare functioning PanNETs. VIPoma cause the Verner-Morrison syndrome. The glucagonoma syndrome is characterized by the triad of necrolytic migratory erythema, diabetes mellitus, and weight loss. Serotonin-producing PanNETs with carcinoid syndrome have to be distinguished from metastatic NETs of the ileum. ACTH-producing tumors with Cushing syndrome are particular aggressive neoplasms (PMID: 25353285).

Molecular Pathology and Genetics

Aurel Perren & Ilaria Marinoni

Sporadic PanNETs

Well-differentiated PanNETs differ fundamentally from PanNECs also regarding their genetics and epigenetics and are therefore discussed separately.

PanNETs are characterized by low **mutation** rates (frequently <1/MB). Classical oncogenic driver mutations are not among the main drivers. In nonfunctioning PanNETs, the tumor suppressor genes with recurrent mutations are involved in chromatin remodeling, telomere length maintenance, and mTOR signaling (Table 5) (Scarpa et al. 2017). Nonfunctioning PanNETs mutated in *DAXX* or *ATRX* are characterized by the ALT (alternative lengthening of telomeres) phenotype, a telomerase independent mechanism of telomere length maintenance (Jiao et al. 2011), chromosomal instability (Marinoni et al. 2014), and increased risk of relapse after surgical resection (Marinoni et al. 2014). Immunohistochemical loss of nuclear DAXX or ATRX staining shows a high correlation to mutations and the prognostic significance has been confirmed by multiple independent series and a large multi-institutional case collection (Hackeng et al. 2021). These stainings are becoming

Table 5 Molecular genetics of PanNENs.

	Gene	Germline or somatic	Frequency
MEN1	MEN1	Somatic and germline	40% / 6%
Altered telomere length	DAXX	Somatic	25%
	ATRX	Somatic	10%
mTOR pathway	PTEN	Somatic	7%
	TSC1/2	Somatic and germline	2% / rare
	DEPDC5	Somatic	2%
Chromatin modification	SETD2	Somatic	5%
	MLL3	Somatic	5%
DNA damage repair	MUTYH	Germline	6%
	CHEK2	Germline	4%
	BRCA2	Germline	1%
Pseudohypoxia	VHL	Germline	rare

good pathology practice and may pave the way for adjuvant trials in PanNET patients.

In addition, **chromosomal copy number alterations** are of clear importance in nonfunctioning PanNETs. *MEN1* mutations alone are frequently associated with limited LOH affecting chromosome 11 and good prognosis (Lawrence et al. 2018). *DAXX* or *ATRX* mutation, often together with *MEN1*, show a recurrent pattern of multiple chromosomal losses (Scarpa et al. 2017; Speel et al. 1999). Interestingly, aneuploid PanNETs with whole genomic gains are not associated to a specific mutation. Only *YY1* is recurrently mutated in 30% of insulinomas. The resulting increased expression of YY1 is associated with a change in mitochondrial metabolism including increased expression of UCP2 and IDH3A (Cao et al. 2013). Intriguingly, most insulinomas have no recurrent mutation or chromosomal alteration.

Epigenetic changes seem to have a crucial role in driving PanNET progression and in shaping molecular and clinical characteristics. Epigenetic profiles are able to distinguish PanNETs with different genetic background, cell of origin, and clinical characteristics (Cejas et al. 2019; Chan et al. 2018; Di Domenico et al. 2020). Notably, DNA methylation discriminates between α-like tumor, epigenetically very similar to α-cells, intermediate tumors which progressively loose differentiation but retain epigenetic similarities with α-cell. β-like tumors are epigenetically close to β-cell, epigenetic similarities to other pancreatic endocrine cell types are not examined yet. α-like tumors are small indolent NF-PanNETs with low risk of relapse, enriched for *MEN1* mutations. Intermediate tumors are larger, with higher grade and high risk of relapse and enriched for alterations in *MEN1* and *DAXX/ATRX*, suggesting a progression from α-like tumors to intermediate (Figure 6). β-like tumors are instead mainly insulinomas. Interestingly, aggressive insulinomas show α–cell transcription factor expression, suggesting a trans-differentiation (Hackeng et al. 2020). α-like and intermediate PanNETs express ARX, while β-like PanNETs are positive for PDX1, further supporting an origin from α and β cells, respectively.

Familial PanNETs

(See also GEP-NENs and Hereditary Syndromes.)

Up to 75% of patients with the MEN1 syndrome due to *MEN1* germline mutations develop PanNETs, most frequently multiple nonfunctional glucagon-producing microtumors (Anlauf et al. 2006b; Nosé et al. 2022; Rindi et al. 2022). Around 15% of von Hippel Lindau syndrome patients will develop nonfunctioning-PanNETs (Blansfield et al. 2007) and these tumors are characterized by pseudohypoxia-signaling and potentially respond to HIF2a inhibitors (Kelley et al. 2022). In patients with Neurofibromatosis Type 1 (NF1), PanNETs are rarely described; these patients can develop duodenal (ampullary) somatostatin-producing NETs that account for up to 30% of this rare tumor. In tuberous sclerosis type 1 and 2, PanNETs are also rarely described.

The rare glucagon cell hyperplasia and neoplasia syndrome is an autosomal recessive disease with inactivating mutations of the Glucagon-receptor GCGR in 50% of the cases (Sipos et al. 2015). In familial insulinomatosis with multiple (micro-) insulinomas, *MAFA* germline mutations are described.

Whole genome sequencing of apparently sporadic PanNETs revealed germline mutations in DNA-repair genes (*MUTYH*, *CHEK2*, and *BRCA2*) in 10% of the patients (Scarpa et al. 2017). *BRCA* and *MUTYH* mutations were associated with respective mutational signatures and with presence of clearly elevated mutational burden (Scarpa et al. 2017).

Poorly Differentiated PanNECs and PanNETs G3

Poorly differentiated PanNECs show **genomic alterations** of *TP53* and *RB1* in over 50% of the cases (Puccini et al. 2020;

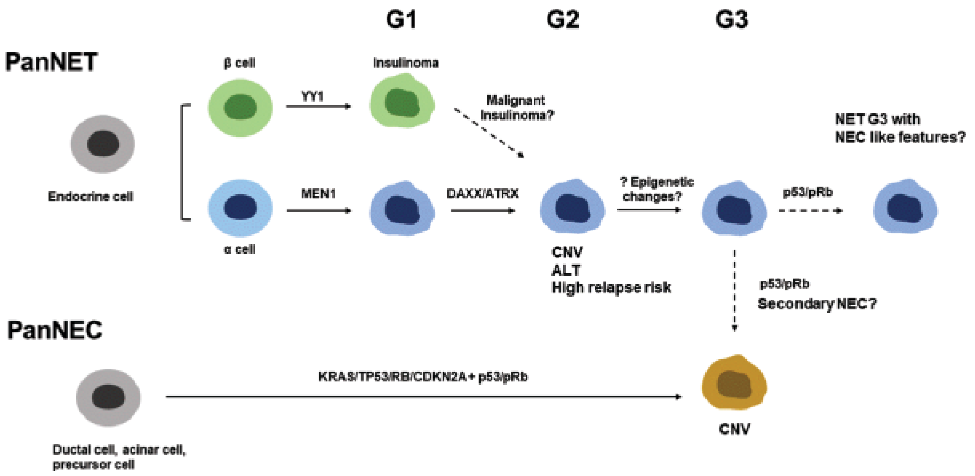

Figure 6 Molecular genetics of PanNENs. For explanations, see text.

Venizelos et al. 2021). In contrast to *TP53*, *RB1* is frequently inactivated by other means than mutations; therefore, Rb immunohistochemistry is better suited than *RB1* mutations analysis to detect its inactivation (Venizelos et al. 2021). Alterations in *KDM5A, MYC, BRAF, KRAS, ARID1A, ESR1, APC*, and *FBXW7* are reported in decreasing frequency between 45% and 10% (Venizelos et al. 2021) of PanNECs. In contrast to colorectal NEC, mismatch repair deficiency is rare.

DNA methylation profiles clearly distinguish PanNETs G3 from PanNECs (Simon et al. 2022). PanNECs are epigenetically closer to acinar cells, positive for the pancreatic progenitor marker SOX9 and negative for ARX and PDX1 suggesting an origin from exocrine or stem cells rather than endocrine cells (Figure 6). On the contrary, PanNETs G3 are epigenetically similar to adult endocrine α and β cells, but occasionally they also express SOX9 indicating also a possible origin from a progenitor cell. A very recent study, based on mutational spectrum and epigenetic profiles, suggested that PanNECs include two different groups of tumors: PanNECs with acinar origin and PanNECs with ductal origin (Yachida et al. 2022).

Clinical Use of Molecular Tools

Molecular characteristics of PanNETs can be exploited in *diagnostic*, *prognostic*, or *predictive* settings. As *DAXX/ATRX* mutations are found almost exclusively in NETs of pancreatic origin, absence of nuclear staining can be used in the clinical setting of a **NET of unknown primary** as strong argument for a pancreatic primary, in conjunction with transcription factor analysis (ISLET1 for pancreas, CDX2 for ileum, TTF1 for lung/thyroid) and expression of hormones (Perren et al. 2017). A future role of epigenetic analyses using methylation signatures in this situation can be anticipated (Di Domenico et al. 2020).

In the setting of high-grade PanNENs with ambiguous morphological features (10–30% of PanNENs), mutations in classical NET drivers are a strong diagnostic argument for the presence of a NET G3. Mutations in adenocarcinoma drivers, *TP53*, and/or Rb protein loss are an argument for NECs (Venizelos et al. 2021); in this situation immunohistochemical analysis of the respective genes is considered state of the art and molecular panels can help in selected cases. Rarely, also NETs G3 as defined by originating from a low-grade NET can acquire *TP53* mutations and even Rb loss, it is a philosophical question as whether to classify such tumors as NETs G3 with NEC like features, or as secondary NEC (in analogy to secondary glioblastomas) (Figure 7). Only limited but promising data on a potential future role of methylation arrays in delineating NET G3 from NEC is emerging (Simon et al. 2022).

On the **prognostic** side, DAXX and ATRX loss of nuclear expression helps defining PanNETs with an increased risk of relapse, as does the ALT phenotype, detected by FISH. Ki-67 still remains the basis for clinical decision and is the most widely used marker. While chromosomally stable PanNETs have been known for many years to carry a very good prognosis (Jonkers et al. 2004; Zhao et al. 2002), this has never found its way to clinical use. Following the example of brain tumors, novel epigenetic methylation-based subtypes of PanNETs with very low relapse risk, described as β-like PanNETs, may be of potential clinical value in the future (Chan et al. 2018; Di Domenico et al. 2020). If confirmed by other series, patients with these tumors may need a less stringent follow up.

While large sequencing panels only rarely detect **treatment targets** in metastasized PanNETs (van Riet et al. 2021), up to 50% of metastasized PanNECs reveal potentially targetable mutations (Puccini et al. 2020; Venizelos et al. 2021), and liquid biopsy also seems to be good starting material for this question (Venizelos, submitted).

In summary, molecular changes are increasingly implemented in diagnosis, definition of prognosis, and indication of specific therapies and this process is expected to get more important in the future.

Clinical Presentation and Diagnosis

Matthias Schott

Nonfunctioning Neuroendocrine Tumors of the Pancreas

Symptoms and Clinical Signs

Non-functioning PanNETs lack symptoms related to hormonal hypersecretion. These tumors are diagnosed late in the course of the disease. Early lesions may not occlude the pancreatic ducts and may remain asymptomatic for many years (Kaltsas et al. 2004). However, when patients harboring such tumors come to medical attention, they have large-sized tumors (primary lesion greater than 5 cm), and 60–80% have already developed synchronous liver metastases (Barakat et al. 2004; Oberg 2004). Primary tumors are mostly localized in the head of the pancreas, followed by the body and tail. Clinical signs and symptoms develop due to the extensive tumor mass, local invasion and compression of nearby structures, and/or the development of distant metastases (Oberg 2004). Common presenting symptoms are abdominal pain (35–80%), followed by weight loss (20–35%), and anorexia and nausea (45%). Less commonly, patients may present with intra-abdominal hemorrhage (4–20%), jaundice (17–50%), and/or a palpable mass (7–40%) (Kaltsas et al. 2004; Oberg 2004). Although the great majority of PanNETs are sporadic, they can also occur in the context of familial (hereditary) syndromes (*see* **below**). In these cases, tumors can be multiple and appear at different stages during the course of the disease (Ramage et al. 2005).

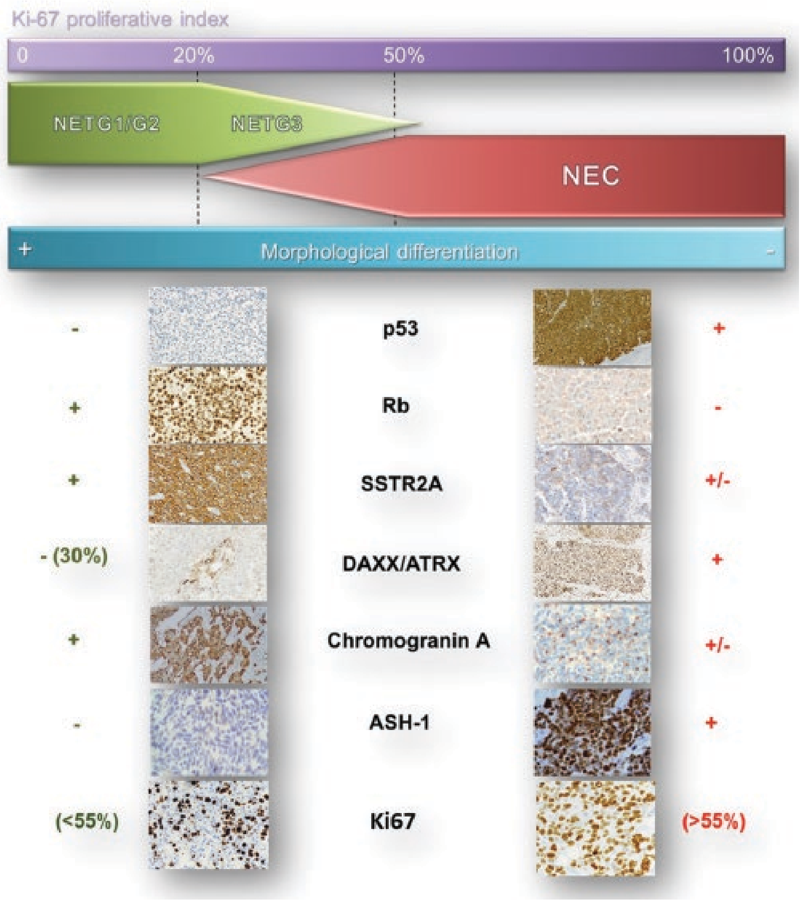

Figure 7 Immunohistochemical markers useful for the differential diagnosis between neuroendocrine tumor (NET) and neuroendocrine carcinoma (NEC). DAXX/ATRX is employed in pancreatic neoplasms: when its expression is lost, it favors NET versus NEC and it has a worsening prognostic impact. Achaete-scute homolog 1 (ASH-1) is an additional general neuroendocrine marker preferentially expressed in NECs rather that in NETs. Regarding Ki67, a threshold that separates high-grade NETs and NECs has not been recognized; however, it has been reported that most of high-grade NETs have a Ki67 proliferation index lower than 55%. (modified from Uccella et al. 2018).

Insulinoma

Symptoms and Clinical Signs

Hypoglycemia is the major symptom of insulinoma. Patients present with nonspecific, episodic hypoglycemic symptoms, which fall into two categories: neuroglycopenic or autonomic (catecholamine/neurogenic). Neuroglycopenia occurs when plasma glucose levels fall below 2.2 mmol/l and is due to central nervous system glucose deprivation. Common symptoms are headache, diplopia, confusion, dizziness, blurred vision, abnormal behavior, lethargy, amnesia. Seizures and coma rarely occur. Symptoms resulting from the activated autonomic nervous system are for instance sweating, weakness, hunger, tremor, nausea, feelings of warmth, anxiety, and palpitations.

Diagnosis

The symptoms of hypoglycemia are nonspecific. Objective measurement of hypoglycemia during a symptomatic period with relief following administration of glucose (Whipple's triad) is strongly suggestive of endogenous hyperinsulinemia. The combination of hypoglycemic symptoms with biochemical hypoglycemia (blood glucose less than 2.2 mmol/l), C-peptidaemia (above 200 pmol/l), and hyperinsulinemia (above 30 pmol/l or 6 mU/l) is pathognomonic of an insulinoma. The Endocrine Society has defined the following criteria for diagnosing endogenous hyperinsulinemia: glucose <3,0 mmol/l, insulin ≥ 18 pmol/l, and C-peptide ≥ 0.2 pmol/l. Fulfilling the glucose and C-peptide criteria, Ahn et al. showed a 100% sensitivity and 8% specificity, while fulfilling the glucose and insulin criteria, they showed 100% sensitivity and 72% specificity (Ahn et al. 2014). All this should be performed within a 72-hour fasting test, which is the gold standard for establishing the diagnosis of insulinoma. The test should start with an oral glucose tolerance test (OGTT) using 75 g glucose given orally with measurement of glucose, insulin, and C-peptide every hour. If the glucose levels are normal during the test, a hypoglycemic disorder is excluded and no further investigation is necessary (de Herder 2004; Okabayashi et al. 2013).

Rare Functioning PanNET

VIPoma

Symptoms and Clinical Signs

The VIPoma syndrome (Vermer–Morrison syndrome) is caused by excessive VIP secretion from the tumor, although other substances can be also secreted. Watery diarrhea occurs in nearly all patients and is frequently produced in excess of 3 liters per day. The diarrhea is secretory and typically persist despite 48–72 hours of fasting.

Diagnosis

The VIPoma syndrome can be difficult to diagnose as other conditions may mimic its presentation, e.g., laxative abuse and Zollinger-Ellison syndrome. These can be differentiated using a careful history and by measurement of gastric pH, acid production, and circulating levels of gastrin and VIP. Fasting plasma VIP levels in healthy volunteers are generally low, while many patients with symptomatic VIPoma have levels more than three times the upper limit of normal.

Glucagonoma

Symptoms and Clinical Signs

The glucagonoma syndrome includes the association of necrolytic migratory erythema, weight loss (often severe), and diabetes. The painful pruritic rash is a typical feature of the glucagonoma syndrome and one of the most common presenting signs, occurring in about 70–80% of patients. Other clinical manifestations include thromboses, cheilitis and glossitis, anemia, and neuropsychiatric symptoms (Frankton and Bloom 1996; Mallinson et al. 1974; Wermers et al. 1996). These symptoms and signs are in relation either directly or indirectly to excessive secretion of glucagon. At the time of diagnosis, more than 80% of the patients already show a metastatic state (Frankton and Bloom 1996; Mallinson et al. 1974; Wermers et al. 1996).

Diagnosis

Raised fasting plasma glucagon immunoreactivity is the basis for diagnosis. False positive results may occur due to other causes of a raised fasting plasma glucagon such as renal or hepatic failure, drugs, and prolonged fasting. Plasma glucagon levels may be elevated to various degrees ranging from only 1.5 to 150 time the upper limit of normal. Thus, if clinically supported, a marginally elevated plasma glucagon level may still be suspicious.

Other Functioning Pancreatic Endocrine Tumors

There are also other types of functioning PanNETs. These are, however, rare and include somatostatinomas and tumors secreting the following hormones: ACTH (ACTHomas), GRF (GRFomas), PTH (PTHomas), and serotonin (pancreatic "carcinoids"). Symptoms depend on the hormone secretion such as Cushing's syndrome in case of ACTH production or symptoms of severe hypercalcemia in PTH secreting tumors.

Diagnostic Imaging

Clarisse Dromain & Nicolas Villard

CT is the first-line imaging modality in the evaluation of patients with suspected PanNENs allowing the investigation of the pancreas as well as the assessment of the disease extension. CT imaging should include 4-phasic imaging including not enhanced arterial/pancreatic phase, venous phase, and delayed phase. The late arterial (30 s) or pancreatic phase (40 s) is mandatory, allowing an increased detection of small functioning PanNETs, in particular insulinomas (Fidler et al. 2003). Moreover, it also improves the detection of hepatic metastases (Dromain et al. 2003). The delayed phase is complementary to the arterial/pancreatic and the venous phase allowing the detection of delayed enhancement of some fibrous tumors (Ichikawa et al. 2000).

MR imaging protocol should include a T1W and T2W sequence with fat suppression, dynamic 3D sequence before and after Gd-chelate contrast-agent injection with multiarterial, venous, and delayed (>5 min) acquisition and DWI sequence. Fat suppression on T1W and T2W images is useful to emphasize the signal intensity differences between the pancreatic tumor and the normal pancreatic tissue. Similarly to CT, T1W delayed (>5 min) images are required to improve both characterization and detection (Ichikawa et al. 2000). Diffusion-weighted images increase the sensitivity for the detection of the primary pancreatic tumor as well as associated liver metastases (d'Assignies et al. 2013). Moreover, ADC values measured from DWI images have recently been identified as a biomarker of tumor aggressiveness correlated with the histological grade of PanNETs. In a recent paper, low ADC was a strong predictor of high tumor grade. A cutoff of 1.19 10^3 mm^2/s was associated with a sensitivity of 100% and a specificity of 92% (Lotfalizadeh et al. 2016).

Imaging features are depending on whether the tumor is functioning or nonfunctioning. Functioning PanNETs are most often manifested by endocrine symptoms with an established or highly suspected clinical and biological diagnosis. The challenge of imaging is to localize the tumor that is often of small size. Most insulinomas are under 2 cm in size, solitary, and benign. They are located all over the pancreatic gland. On CT images, typical insulinomas are well-defined, hypervascular, and show intense enhancement during arterial/pancreatic phase. The enhancement is usually uniform. Sometime, a rim enhancement is considered highly suggestive of the diagnosis (Sheth et al. 2002). Gastrinoma are also small pancreatic tumor (1–3 cm) arising in 80% within the "gastrinoma triangle" (defined as the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially). Gastrinomas are the PanNETs more often associated with MEN1 syndrome. In these cases, they are often multicentric, and are associated with a major morbidity and mortality. After contrast injection, gastrinomas have more often a delayed enhancement persistent on delayed phase due to presence of fibrosis. Other presentations of functioning PanNETs include purely cystic tumors in 10%, commonly associated with MEN1, complex solid and cystic pattern, and calcified tumors in less than 5% (Gallotti et al. 2013).

On MRI, most of functioning PanNETs show low signal intensity on T1W, high signal intensity on T2W images, and intense and early enhancement on dynamic T1W sequence after injection. Hypervascular tumors (typically, insulinoma) are often better depicted on the T2W with fat suppression, whereas hypovascular tumors are better depicted on the T1W sequence in the arterial phase. This is probably explained by the high enhancement of the pancreas in the arterial phase, which can mask hypervascular tumors, whereas non-hypervascular tumors are surrounded by the enhanced normal pancreatic parenchyma (Caramella et al. 2010). The finding of a well-circumscribed hypervascular mass with homogeneous enhancement is more common in grade 1 tumors. On the contrary, an ill-defined hypovascular tumor on the arterial and portal phase with heterogeneous enhancement is more common in grade 2/3 NETs or NECs (Kim et al. 2013; Takumi et al. 2015). Diffusion-weighted imaging is helpful to detect small PanNETs due to its greater image contrast. ADC values have been shown to be lower than in adjacent pancreatic parenchyma in all cases of solid nodules (Caramella et al. 2010). However, higher ADC values can be obtained in case of cystic pattern (Brenner et al. 2012).

Nonfunctioning PanNETs are often detected incidentally or have nonspecific symptoms. The challenge of imaging is to differentiate PanNET from ductal adenocarcinoma or other type of pancreatic tumors and to determine the extent and the potential of resectability. On CT and MR images, nonfunctioning PanNET appears as a large pancreatic mass with heterogeneous enhancement due to necrotic and hemorrhagic changes. On MR images, in contrast to pancreatic adenocarcinoma, most of PanNETs are hyperintense on T2W images and hyper- or isointense during the arterial/pancreatic phase of the dynamic study (Manfredi et al. 2013). Moreover, PanNETs tend to have a higher rate of tumoral vein thrombosis (splenic, portal, and superior mesenteric veins) and a lower rate of vascular encasement than pancreatic adenocarcinoma (Caramella et al. 2010; Manfredi et al. 2013). Dilatation of the upstream pancreatic and common bile duct is rarer than in pancreatic adenocarcinoma and is detected in 33% of cases for the main pancreatic duct and less than 9% for the common bile duct (Kim et al. 2016).

Surgical Treatment

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Surgical treatment of patients with PanNENs has evolved significantly over the past few decades, but still selecting the best treatment option remains a complex challenge for surgeons. The indication and extent of surgical resection of PanNENs can vary considerably depending on factors such as tumor size and grade, hormone production, local and systemic tumor spread, tumor location within the gland, association with hereditary syndromes, as well as patient age and comorbidities. Given this complex situation, accurate preoperative assessment of the patient and interdisciplinary discussion of the findings in a multidisciplinary team meeting are essential for determining the optimal management of PanNEN patients. Once surgical resection is indicated, treatment options range from minimally invasive tumor enucleations, which can be performed for insulinomas, to multivisceral resections for locally advanced or metastatic tumors. In the following sections, the indications for surgical resection as well as surgical procedures currently used to treat patients with different types and stages of PanNENs will be systematically presented.

Indications for Surgical Resection of PanNENs

Basically, all patients with PanNENs should be evaluated for surgical resection, which represents the cornerstone of curative treatment. The indication for surgery largely depends on the type of PanNENs (nonfunctional or functional) as well as the preoperative staging (local tumor stage and metastatic spread). Preoperative evaluation of the patient for hormonal activity of the neoplasia and a thorough radiologic staging, which should include a CT scan, somatostatin receptor scintigraphy, or PET/CT with ^{68}Gallium as well as an endosonography and MR cholangiopancreatography in case of a planned enucleation, are therefore fundamental requirements for a good indication in patients with pancreatic neuroendocrine neoplasia (Partelli et al. 2017a).

Functional and Nonfunctional PanNENs

For functionally active and nonfunctional PanNENs > 2 cm, pancreatic resection is the standard of treatment (Falconi et al. 2016; Pavel et al. 2020). However, in asymptomatic patients with nonfunctional PanNENs ≤ 2 cm, recent studies demonstrated the safety of a watch-and-wait strategy instead of surgery (Gaujoux et al. 2013; Partelli et al. 2017b). Accordingly, current guidelines support the use of conservative therapy consisting of periodically repeated high-quality imaging (every 6–12 month) for nonfunctional PanNENs ≤ 2 cm in patients with significant comorbidities, advanced age, unfavorable tumor location, or affected by MEN1 (Falconi et al. 2016; Partelli et al. 2017a; Pavel et al. 2020). However, in young patients and cases with signs of local invasiveness (dilatation of the main pancreatic duct, presence of jaundice, suspected nodal involvement) resection for nonfunctional PanNENs ≤ 2 cm is recommended (Falconi et al. 2016; Pavel et al. 2020). Surgical resection should generally be considered for insulinomas. If possible, a parenchyma-sparing minimally invasive procedure should be preferred (Vanderveen and Grant 2010). However, in the rare case of malignant insulinoma, pancreatectomy with lymphadenectomy is recommended (Akerstrom and Hellman 2007). All other functional pancreatic NENs (gastrinomas, glucagonomas, VIPomas, somatostatinomas, GRFomas, PPomas, ACTHomas, and PTHomas) are at high risk for malignancy, thus pancreatectomy with lymphadenectomy is highly advised (Doi 2015). MEN1 associated gastrinomas frequently develop metachronous recurrences, so excessive surgery should be avoided if reasonable (Albers et al. 2019).

Tumor Grading and Stage

Surgery represents the treatment of choice for locally or locoregionally limited G1 and G2 PanNETs (Falconi et al. 2016; Pavel et al. 2020). PanNET patients also benefit from surgical resection when lymph node metastases are present or large adjacent vessels are involved (Bartsch et al. 2012; Haugvik et al. 2013; Norton et al. 2011). In addition, multivisceral resection is warranted in selected patients with G1 and G2 tumors that have invaded adjacent organs (colon, stomach, adrenal gland) (Partelli et al. 2017a). However, in line with the classification proposed for resectability of pancreatic adenocarcinoma, PanNETs with encasement of the superior mesenteric artery (SMA), celiac axis (CA), or common hepatic artery (CHA) should be considered unresectable (Partelli et al. 2017a). In the presence of G1 and G2 PanNETs with resectable liver metastases and absence of extra-abdominal metastatic disease, a surgical approach is recommended (Frilling et al. 2014; Howe et al. 2020; Partelli, Bartsch 2017a), whereas the role of palliative debulking in G1 and G2 PanNET patients with unresectable liver metastases is controversial (Howe et al. 2020). To date, only limited data exist regarding the indication for surgical resection in patients with highly proliferative G3 PanNETs and poorly differentiated pancreatic neuroendocrine carcinoma (PanNEC). While curative surgery appears to improve the prognosis of patients with G3 PanNETs, its benefit in localized PanNECs remains unclear (Merola et al. 2020; Yoshida et al. 2019). However, since surgical resection is the only option for curative treatment in localized PanNECs, the indication for surgery can be made in selected cases after detailed patient information as part of an individual decision. Whereas a surgical approach can be discussed for advanced NETs G3 with resectable liver metastasis, advanced metastatic PanNECs represent an absolute contraindication for surgical resection (Pavel et al. 2020; Souche et al. 2020).

Modalities of Surgical Treatment for PanNENs

Standard Pancreatic Resection and Parenchyma-sparing Pancreatic Resection

Standard surgical procedures used for the treatment of PanNENs include partial pancreaticoduodenectomy (PPD) and distal pancreatectomy (DP) with lymph node dissection. These extensive interventions are associated with considerable morbidity, as well as impaired exocrine and endocrine pancreatic function. To address these drawbacks, parenchyma-sparing pancreatic resections such as enucleation and central pancreatectomy have been applied to treat the commonly less aggressive G1 and G2 PanNETs (Goudard et al. 2014; Jilesen et al. 2016). However, the risk of inadequate resection margin and the lack of lymphadenectomy are major limitations of these procedures. In addition, parenchymal-sparing resections were found to be associated with similar postoperative fistula rates and mortality when compared with standard resections. For these reasons, the indication for performing parenchyma-sparing pancreatic resections should be limited to small (≤2 cm) insulinomas and small (≤2 cm) nonfunctioning-PanNETs (Partelli et al. 2017a). Enucleation can be performed in superficial PanNETs without involvement of the pancreatic duct (distance > 2–3 mm) (Howe et al. 2020; Partelli et al. 2017a). Therefore, prior to performing this procedure, an affection of the pancreatic duct by the tumor should be excluded by MR cholangiopancreatography and endoscopic ultrasound in order to minimize the risk of postoperative pancreatic fistula (Partelli et al. 2017a). Central pancreatectomy can be performed for tumors in the pancreatic body without involvement of the gastroduodenal artery or common bile duct. Regarding morbidity associated with the presence of two pancreatic resection sites, the length of the preserved pancreatic tail (generally > 5 cm) and the patient's actual pancreatic function (presence and severity of diabetes) should be considered when weighing the benefits and risks of central versus distal pancreatectomy (Howe et al. 2020).

Lymphadenectomy during Pancreatic Resection for PanNENs

The optimal extent of lymphadenectomy during resection for PanNENs and the association between nodal metastasis and overall survival are still controversial. Current guidelines recommend regional lymphadenectomy, including at least peripancreatic and SMA nodes, as part of the pancreatic resection in PanNETs > 2 cm. At least 12 lymph nodes should be removed (Gaujoux et al. 2013; Howe et al. 2020). Atypical, parenchyma-sparing pancreatic resections for PanNETs ≤ 2 are associated with a significantly lower lymph node removal than standardized resections (Parekh et al. 2012). However, PanNETs ≤ 2 cm are at considerable risk of lymph node involvement, thus nodal sampling and frozen section procedure should be routinely performed, especially if suspicious lymph nodes are present.

Intraoperative evidence of nodal involvement should prompt the surgeon to choose a standard pancreatic resection, rather than the atypical procedure (Partelli et al. 2017a).

Laparoscopic and Robotic Surgery in PanNENs

Due to the high degree of technical difficulty, minimally invasive pancreatic surgery has been developing slowly. In particular, reconstruction after PPD is a major challenge laparoscopically. So far, published studies have failed to demonstrate that laparoscopic surgery is superior or even equivalent to the open approach in PPD. One randomized controlled trial was even terminated early because mortality was significantly increased in the laparoscopic group (van Hilst et al. 2019). In contrast to laparoscopy, the use of robotic surgery seems to have certain advantages over the open approach in PPD (less blood loss, fewer major complications) (Zureikat et al. 2016). However, at this time, robotic PPD should only be performed in centers with extensive experience in open and minimally invasive pancreatic surgery (Howe et al. 2020). By contrast, recent studies analyzing minimally invasive pancreatic resections that do not require reconstruction, including DP and enucleation, appear much more encouraging. Numerous studies indicate that laparoscopic DP and enucleation are superior to open surgery in selected patients with regard to functional recovery, intraoperative blood loss, and postoperative complications (de Rooij et al. 2019; Drymousis et al. 2014; Howe et al. 2020; Mehrabi et al. 2014). However, patients with larger tumors (> 8 cm), significant lymphadenopathy, vascular involvement, or requiring multi-visceral resection are likely to benefit from open surgery (Howe et al. 2020). Comparing the laparoscopic and robotic approaches in DP and enucleation, recent studies show little difference, except that robotic surgery appears to be associated with a lower conversion rate (Guerrini et al. 2017).

References

Ahn, C.H., Kim, L.K., Lee, J.E. et al. (2014). Clinical implications of various criteria for the biochemical diagnosis of insulinoma. *Endocrinol Metab (Seoul)* 29 (4): 498–504.

Akerstrom, G. and Hellman, P. (2007). Surgery on neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab* 21 (1): 87–109.

Albers, M.B., Manoharan, J., Bollmann, C. et al. (2019). Results of duodenopancreatic reoperations in multiple endocrine neoplasia type 1. *World J Surg* 43 (2): 552–558.

Anlauf, M., Bauersfeld, J., Raffel, A. et al. (2009). Insulinomatosis: a multicentric insulinoma disease that frequently causes early recurrent hyperinsulinemic hypoglycemia. *Am J Surg Pathol* 33 (3): 339–346.

Anlauf, M., Garbrecht, N., Bauersfeld, J. et al. (2007). Hereditary neuroendocrine tumors of the gastroenteropancreatic system. *Virchows Arch* 451 (Suppl 1): S29–38.

Anlauf, M., Garbrecht, N., Henopp, T. et al. (2006a). Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. *World J Gastroenterol* 12 (34): 5440–5446.

Anlauf, M., Schlenger, R., Perren, A. et al. (2006b). Microadenomatosis of the endocrine pancreas in patients with and without the multiple endocrine neoplasia type 1 syndrome. *Am J Surg Pathol* 30 (5): 560–574.

Barakat, M.T., Meeran, K., and Bloom, S.R. (2004). Neuroendocrine tumours. *Endocr Relat Cancer* 11 (1): 1–18.

Bartsch, D.K., Waldmann, J., Fendrich, V. et al. (2012). Impact of lymphadenectomy on survival after surgery for sporadic gastrinoma. *Br J Surg* 99 (9): 1234–1240.

Basturk, O., Tang, L., Hruban, R.H. et al. (2014). Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. *Am J Surg Pathol* 38 (4): 437–447.

Blansfield, J.A., Choyke, L., Morita, S.Y. et al. (2007). Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). *Surgery* 142 (6): 814–818; discussion 8 e1-2.

Brenner, R., Metens, T., Bali, M. et al. (2012). Pancreatic neuroendocrine tumor: added value of fusion of T2-weighted imaging and high b-value diffusion-weighted imaging for tumor detection. *Eur J Radiol* 81 (5): E746–E9.

Cao, Y., Gao, Z., Li, L. et al. (2013). Whole exome sequencing of insulinoma reveals recurrent T372R mutations in YY1. *Nat Commun* 4: 2810.

Caramella, C., Dromain, C., Baere, T. et al. (2010). Endocrine pancreatic tumours: which are the most useful MRI sequences? *Eur Radiol* 20 (11): 2618–2627.

Cejas, P., Drier, Y., Dreijerink, K.M.A. et al. (2019). Enhancer signatures stratify and predict outcomes of non-functional pancreatic neuroendocrine tumors. *Nat Med* 25 (8): 1260–1265.

Chan, C.S., Laddha, S.V., Lewis, P.W. et al. (2018). ATRX, DAXX or MEN1 mutant pancreatic neuroendocrine tumors are a distinct alpha-cell signature subgroup. *Nat Commun* 9 (1): 4158.

d'Assignies, G., Fina, P., Bruno, O. et al. (2013). High sensitivity of diffusion-weighted MR imaging for the detection of liver metastases from neuroendocrine tumors: comparison with T2-weighted and dynamic gadolinium-enhanced MR imaging. *Radiology* 268 (2): 390–399.

Das, S. and Dasari, A. (2021). Epidemiology, incidence, and prevalence of neuroendocrine neoplasms: are there global differences? *Curr Oncol Rep* 23 (4): 43.

Dasari, A., Mehta, K., Byers, L.A. et al. (2018). Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: a SEER database analysis of 162,983 cases. *Cancer* 124 (4): 807–815.

de Herder, W.W. (2004). Insulinoma. *Neuroendocrinology* 80 (Suppl 1): 20–22.

de Rooij, T., van Hilst, J., van Santvoort, H. et al. (2019). Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. *Ann Surg* 269 (1): 2–9.

Di Domenico, A., Pipinikas, C.P., Maire, R.S. et al. (2020). Epigenetic landscape of pancreatic neuroendocrine tumours reveals distinct cells of origin and means of tumour progression. *Commun Biol* 3 (1): 740.

Doi, R. (2015). Determinants of surgical resection for pancreatic neuroendocrine tumors. *J Hepatobiliary Pancreat Sci* 22 (8): 610–617.

Dromain, C., de Baere, T., Baudin, E. et al. (2003). MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *AJR Am J Roentgenol* 180 (1): 121–128.

Drymousis, P., Raptis, D.A., Spalding, D. et al. (2014). Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis. *HPB (Oxford)* 16 (5): 397–406.

Falconi, M., Eriksson, B., Kaltsas, G. et al. (2016). ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *neuroendocrinology* 103 (2): 153–171.

Fidler, J.L., Fletcher, J.G., Reading, C.C. et al. (2003). Preoperative detection of pancreatic insulinomas on multiphasic helical CT. *AJR Am J Roentgenol* 181 (3): 775–780.

Frankton, S. and Bloom, S.R. (1996). Gastrointestinal endocrine tumours. Glucagonomas. *Baillieres Clin Gastroenterol* 10 (4): 697–705.

Frilling, A., Modlin, I.M., Kidd, M. et al. (2014). Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 15 (1): e8–21.

Gallotti, A., Johnston, R.P., Bonaffini, P.A. et al. (2013). Incidental neuroendocrine tumors of the pancreas: MDCT findings and features of malignancy. *AJR Am J Roentgenol* 200 (2): 355–362.

Garbrecht, N., Anlauf, M., Schmitt, A. et al. (2008). Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. *Endocr Relat Cancer* 15 (1): 229–241.

Gaujoux, S., Partelli, S., Maire, F. et al. (2013). Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 98 (12): 4784–4789.

Goudard, Y., Gaujoux, S., Dokmak, S. et al. (2014). Reappraisal of central pancreatectomy a 12-year single-center experience. *JAMA Surg* 149 (4): 356–363.

Guerrini, G.P., Lauretta, A., Belluco, C. et al. (2017). Robotic versus laparoscopic distal pancreatectomy: an up-to-date meta-analysis. *BMC Surg* 17 (1): 105.

Hackeng, W.M., Brosens, L.A.A., Kim, J.Y. et al. (2021). Non-functional pancreatic neuroendocrine tumours: ATRX/DAXX and alternative lengthening of telomeres (ALT) are prognostically independent from ARX/PDX1 expression and tumour size. *Gut* 71 (5): 961–973.

Hackeng, W.M., Morsink, F.H.M., Moons, L.M.G. et al. (2020). Assessment of ARX expression, a novel biomarker for metastatic risk in pancreatic neuroendocrine tumors, in endoscopic ultrasound fine-needle aspiration. *Diagn Cytopathol* 48 (4): 308–315.

Hallet, J., Law, C.H., Cukier, M. et al. (2015). Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 121 (4): 589–597.

Haugvik, S.P., Labori, K.J., Waage, A. et al. (2013). Pancreatic surgery with vascular reconstruction in patients with locally advanced pancreatic neuroendocrine tumors. *J Gastrointest Surg* 17 (7): 1224–1232.

Hauso, O., Gustafsson, B.I., Kidd, M. et al. (2008). Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer* 113 (10): 2655–2664.

Heetfeld, M., Chougnet, C.N., Olsen, I.H. et al. (2015). Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 22 (4): 657–664.

Howe, J.R., Merchant, N.B., Conrad, C. et al. (2020). The North American neuroendocrine tumor society consensus paper on the surgical management of pancreatic neuroendocrine tumors. *Pancreas* 49 (1): 1–33.

Ichikawa, T., Peterson, M.S., Federle, M.P. et al. (2000). Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. *Radiology* 216 (1): 163–171.

Jiao, Y., Shi, C., Edil, B.H. et al. (2011). DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 331 (6021): 1199–1203.

Jilesen, A.P., van Eijck, C.H., Busch, O.R. et al. (2016). Postoperative outcomes of enucleation and standard resections in patients with a pancreatic neuroendocrine tumor. *World J Surg* 40 (3): 715–728.

Jonkers, Y.M., Claessen, S.M., Komminoth, P. et al. (2004). Genomic alterations in benign and malignant insulinomas as revealed by conventional and array CGH. *Proc Am Assoc Cancer Res Annual Meeting* 45: 654.

Kaltsas, G.A., Besser, G.M., and Grossman, A.B. (2004). The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev* 25 (3): 458–511.

Kapran, Y., Bauersfeld, J., Anlauf, M. et al. (2006). Multihormonality and entrapment of islets in pancreatic endocrine tumors. *Virchows Arch* 448 (4): 394–398.

Kasajima, A., Konukiewitz, B., Schlitter, A.M. et al. (2022). An analysis of 130 neuroendocrine tumors G3 regarding prevalence, origin, metastasis, and diagnostic features. *Virchows Arch* 480 (2): 359–368.

Kelley, R.K., Van Cutsem, E., Lee, M.S. et al. Phase 2 open-label study of pembrolizumab plus lenvatinib and belzutifan in patients with advanced solid tumors. American Society of Clinical Oncology, ASCO Gastrointestinal Cancers Symposium 2022 (Meeting Abstract).

Kim, J.H., Eun, H.W., Kim, Y.J. et al. (2013). Staging accuracy of MR for pancreatic neuroendocrine tumor and imaging findings according to the tumor grade. *Abdom Imaging* 38 (5): 1106–1114.

Kim, J.H., Eun, H.W., Kim, Y.J. et al. (2016). Pancreatic neuroendocrine tumour (PNET): staging accuracy of MDCT and its diagnostic performance for the differentiation of PNET with uncommon CT findings from pancreatic adenocarcinoma. *Eur Radiol* 26 (5): 1338–1347.

Konukiewitz, B., Enosawa, T., and Klöppel, G. (2011). Glucagon expression in cystic pancreatic neuroendocrine neoplasms: an immunohistochemical analysis. *Virchows Arch* 458 (1): 47–53.

Konukiewitz, B., Jesinghaus, M., Kasajima, A., and Klöppel, G. (2022). Neuroendocrine neoplasms of the pancreas: diagnosis and pitfalls. *Virchows Arch* 480 (2): 247–257.

Konukiewitz, B., Schlitter, A.M., Jesinghaus, M. et al. (2017). Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20. *Mod Pathol* 30 (4): 587–598.

Konukiewitz, B., von Hornstein, M., Jesinghaus, M. et al. (2020). Pancreatic neuroendocrine tumors with somatostatin expression and paraganglioma-like features. *Hum Pathol* 102: 79–87.

Krejs, G.J., Orci, L., Conlon, J.M. et al. (1979). Somatostatinoma syndrome. Biochemical, morphologic and clinical features. *N Engl J Med* 301 (6): 285–292.

Lawrence, B., Blenkiron, C., Parker, K. et al. (2018). Recurrent loss of heterozygosity correlates with clinical outcome in pancreatic neuroendocrine cancer. *NPJ Genom Med* 3 (1): 1–12.

Lee, M.R., Harris, C., Baeg, K.J. et al. (2019). Incidence trends of gastroenteropancreatic neuroendocrine tumors in the united states. *Clin Gastroenterol Hepatol* 17 (11): 2212–7.e1.

Leoncini, E., Carioli, G., La Vecchia, C. et al. (2016). Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. *Ann Oncol* 27 (1): 68–81.

Lotfalizadeh, E., Ronot, M., Wagner, M. et al. (2016). Prediction of pancreatic neuroendocrine tumour grade with MR imaging features: added value of diffusion-weighted imaging. *Eur Radiol* 27 (4): 1748–1759.

Mallinson, C.N., Bloom, S.R., Warin, A.P. et al. (1974). A glucagonoma syndrome. *Lancet* 2 (7871): 1–5.

Manfredi, R., Bonatti, M., Mantovani, W. et al. (2013). Non-hyperfunctioning neuroendocrine tumours of the pancreas: MR imaging appearance and correlation with their biological behaviour. *Eur Radiol* 23 (11): 3029–3039.

Marinoni, I., Kurrer, A.S., Vassella, E. et al. (2014). Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. *Gastroenterology* 146 (2): 453–60 e5.

McCall, C.M., Shi, C., Klein, A.P. et al. (2012). Serotonin expression in pancreatic neuroendocrine tumors correlates with a trabecular histologic pattern and large duct involvement. *Hum Pathol* 43 (8): 1169–1176.

Mehrabi, A., Fischer, L., Hafezi, M. et al. (2014). A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas* 43 (5): 675–686.

Merola, E., Rinke, A., Partelli, S. et al. (2020). Surgery with Radical Intent: is There an Indication for G3 Neuroendocrine Neoplasms? *Ann Surg Oncol* 27 (5): 1348–1355.

Norton, J.A., Harris, E.J., Chen, Y. et al. (2011). Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. *Arch Surg* 146 (6): 724–732.

Nosé, V., Gill, A., Teijeiro, J.M.C. et al. (2022). Overview of the 2022 WHO classification of familial endocrine tumor syndromes. *Endocr Pathol* 33 (1): 197–227.

Oberg, K. (2004). Management of neuroendocrine tumours. *Ann Oncol* 15 (Suppl 4): iv293–8.

Okabayashi, T., Shima, Y., Sumiyoshi, T. et al. (2013). Diagnosis and management of insulinoma. *World J Gastroenterol* 19 (6): 829–837.

Parekh, J.R., Wang, S.C., Bergsland, E.K. et al. (2012). Lymph node sampling rates and predictors of nodal metastasis in pancreatic neuroendocrine tumor resections: the UCSF experience with 149 patients. *Pancreas* 41 (6): 840–844.

Partelli, S., Bartsch, D.K., Capdevila, J. et al. (2017a). ENETS Consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology* 105 (3): 255–265.

Partelli, S., Cirocchi, R., Crippa, S. et al. (2017b). Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *Br J Surg* 104 (1): 34–41.

Pavel, M., Oberg, K., Falconi, M. et al. (2020). Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 31 (7): 844–860.

Perren, A., Couvelard, A., Scoazec, J.Y. et al. (2017). ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. *Neuroendocrinology* 105 (3): 196–200.

Puccini, A., Poorman, K., Salem, M.E. et al. (2020). Comprehensive genomic profiling of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). *Clin Cancer Res* 26 (22): 5943–5951.

Ramage, J.K., Davies, A.H., Ardill, J. et al. (2005). Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 54 (Suppl 4): iv1–16.

Rindi, G., Mete, O., Uccella, S. et al. (2022). Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol* 33 (1): 115–154.

Scarpa, A., Chang, D.K., Nones, K. et al. (2017). Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature* 543 (7643): 65–71.

Scoazec, J.Y., Couvelard, A., Monges, G. et al. (2017). Professional practices and diagnostic issues in neuroendocrine tumour pathology: results of a prospective one-year survey among french pathologists (the PRONET Study). *Neuroendocrinology* 105 (1): 67–76.

Sheth, S., Hruban, R.K., and Fishman, E.K. (2002). Helical CT of islet cell tumors of the pancreas: typical and atypical manifestations. *AJR Am J Roentgenol* 179 (3): 725–730.

Simon, T., Riemer, P., Jarosch, A. et al. (2022). DNA methylation reveals distinct cells of origin for pancreatic neuroendocrine carcinomas and pancreatic neuroendocrine tumors. *Genome Med* 14 (1): 24.

Sipos, B., Sperveslage, J., Anlauf, M. et al. (2015). Glucagon cell hyperplasia and neoplasia with and without glucagon receptor mutations. *J Clin Endocrinol Metab* 100 (5): E783–8.

Souche, R., Hobeika, C., Hain, E., and Gaujoux, S. (2020). Surgical Management of Neuroendocrine Tumours of the Pancreas. *J Clin Med* 9: 9.

Speel, E.J., Richter, J., Moch, H. et al. (1999). Genetic differences in endocrine pancreatic tumor subtypes detected by comparative genomic hybridization. *Am J Pathol* 155 (6): 1787–1794.

Takumi, K., Fukukura, Y., Higashi, M. et al. (2015). Pancreatic neuroendocrine tumors: correlation between the contrast-enhanced computed tomography features and the pathological tumor grade. *EurJ Radiol* 84 (8): 1436–1443.

Tang, L.H., Basturk, O., Sue, J.J., and Klimstra, D.S. (2016). A practical approach to the classification of WHO grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. *Am J Surg Pathol* 40 (9): 1192–1202.

van Hilst, J., de Rooij, T., Bosscha, K. et al. (2019). Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *Lancet Gastroenterol Hepatol* 4 (3): 199–207.

van Riet, J., van de Werken, H.J., Cuppen, E. et al. (2021). The genomic landscape of 85 advanced neuroendocrine neoplasms reveals subtype-heterogeneity and potential therapeutic targets. *Nat Commun* 12 (1): 1–14.

Vanderveen, K. and Grant, C. (2010). Insulinoma. *Cancer Treat Res* 153: 235–252.

Venizelos, A., Elvebakken, H., Perren, A. et al. (2021). The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 29 (1): 1–14.

Wermers, R.A., Fatourechi, V., Wynne, A.G. et al. (1996). The glucagonoma syndrome. Clinical and pathologic features in 21 patients. *Medicine (Baltimore)* 75 (2): 53–63.

WHO Classification of Tumours Editorial Board. (2022). Endocrine and neuroendocrine tumours, [Internet] 5e. Lyon: International Agency for Research on Cancer (IARC). Available from: https://tumourclassification.iarc.who.int/chapters/53 (accessed 28th January 2023).

WHO Classification of Tumours Editorial Board. (2019). *Digestive System Tumours*, 5e. Lyon: International Agency for Research on Cancer (IARC).

Yachida, S., Totoki, Y., Noe, M. et al. (2022). Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system. *Cancer Discov* 12 (3): 692–711.

Yang, M., Zeng, L., Ke, N.W. et al. (2020). World Health Organization grading classification for pancreatic neuroendocrine neoplasms: a comprehensive analysis from a large Chinese institution. *BMC Cancer* 20 (1): 906.

Yoshida, T., Hijioka, S., Hosoda, W. et al. (2019). Surgery for pancreatic neuroendocrine tumor G3 and carcinoma G3 should be considered separately. *Ann Surg Oncol* 26 (5): 1385–1393.

Zhao, J., Roth, J., Bode-Lesniewska, B. et al. (2002). Combined comparative genomic hybridization and genomic microarray for detection of gene amplifications in pulmonary artery intimal sarcomas and adrenocortical tumors. *Genes Chromosomes Cancer* 34 (1): 48–57.

Zureikat, A.H., Postlewait, L.M., Liu, Y. et al. (2016). A multi-institutional comparison of perioperative outcomes of robotic and open pancreaticoduodenectomy. *Ann Surg* 264 (4): 640–649.

Jejunum and Ileum

Epidemiology and Pathology

Bence Sipos

Epidemiology

The incidence of NET in the small intestine (siNETs) has continuously been rising in the last decades. Analysis of the SEER database exhibited an incidence of siNETs of per 100,000 persons in 1973 and 1.25 per 100,000 persons in 2012 (Dasari et al. 2017). Cancer registries outside the US showed mostly lower incidence rates that ranged from 0.12 (Italy) to 1.33/100,000 (Sweden) (Fraenkel et al. 2014).

SiNETs are the most frequent gastroenteropancreatic NETs in the Western world (Ellis et al. 2010; Lawrence et al. 2011) and the second most common NETs in humans following lung carcinoids. In some countries, rectal NETs seem to overtake the first place among gastroenteropancreatic NETs, which is most probably attributable to increasing use of endoscopy (Fraenkel et al. 2014).

The male:female ratio of siNETs is 1.2:1. The mean age of the first diagnosis of siNETs is about 68 years (Ellis et al. 2010).

Pathology

SiNETs are mostly located in the distal ileum, therefore they can be visualized and biopsied using conventional colonoscopy. They are rarely found in the jejunum or in Meckel's diverticulum. Relevant proportion (30–50%) of siNETs can be multiple, showing 2 to >50 tumors (Figure 8). Despite the high rate of multiple siNETS, familial cases are seldom (Gangi et al. 2018; Perez et al. 2021). Tumor size ranges from 1 to 5 cm. Macroscopically, siNETs present broad based flat polypoid white-yellowish lesions (Figure 9 A), that are covered by intact mucosa or may show small central ulcers. Even tiny tumors can be associated with extensive lymph node metastases in the mesentery or in distant organs. Concentric stenosis of the small bowel does not occur due to the primary, nevertheless, bowel obstruction is frequently seen because of mesenteric fibrosis adjacent to lymph node metastases. On microscopic evaluation, siNETs are composed of round monomorphic tumor cells with bland nuclei (Figure 9 B). The nuclear chromatin is finely granulated. Cohesive nest- and island-like growth pattern is typically present. Tumor cells may grow as single cells or smaller cell nests in deeper layers. Disseminated peritoneal carcinosis occurs rather rarely, despite the frequent tumor infiltration into subserosa and serosal surface at primary presentation. Lymphovascular invasion is a common feature.

SiNETs exhibit a characteristic phenotype by immunohistochemistry. Established neuroendocrine markers such as synaptophysin, chromogranin A, and INSM1 are positive in most cases, combined with CDX2, serotonin, and substance P expression (Figure 9 C). Transcription factors TTF1, ISLET1, and SATB2, which are characteristic for neuroendocrine neoplasms of the lung, pancreas, rectum/appendix, respectively, are only infrequently detected in siNETs. Therefore, the immunophenotype including neuroendocrine marker^{+}, CDX2^{+}, Serotonin^{+}, SATB2^{-} largely helps to distinguish between siNETs and NETs of other organs, even in case of metastatic disease without apparent primary tumor (Hoskoppal et al. 2020; Jaffee et al. 2006; McHugh et al. 2020; Schmitt et al. 2008).

The vast majority of siNETs is represented by grade 1 or grade 2 tumors (Jann et al. 2011), showing a Ki67 rate below 20%. However, most cases exhibit a Ki67 rate <4% (Figure 9 D) (Mai et al. 2019). Most remarkably, there is no relevant difference in the proliferation rates in primary tumors and their metastases (Anlauf et al. 2014).

The overwhelming majority of siNETs does express somatostatin receptors (SSTRs). The most common SSTR subtype is SSTR2 followed by SSTR5. SSTR1, SSTR3, and SSTR4 do not exhibit relevant expression by immunohistochemistry (Mai et al. 2019).

Jejunal NETs are rare tumors, representing <5% all small bowel NETs (excluding duodenal NETs). They represent a heterogeneous group, showing either classical enterochromaffin features (like ileal NET), or gastrin-producing well-differentiated NET or even solid/pseudoglandular grade 2 or grade 3 NETs (Chopin-Laly et al. 2013).

Molecular Pathology

Comprehensive sequencing studies have identified siNET as genetically "silent," showing a low mutation rate of 0.1

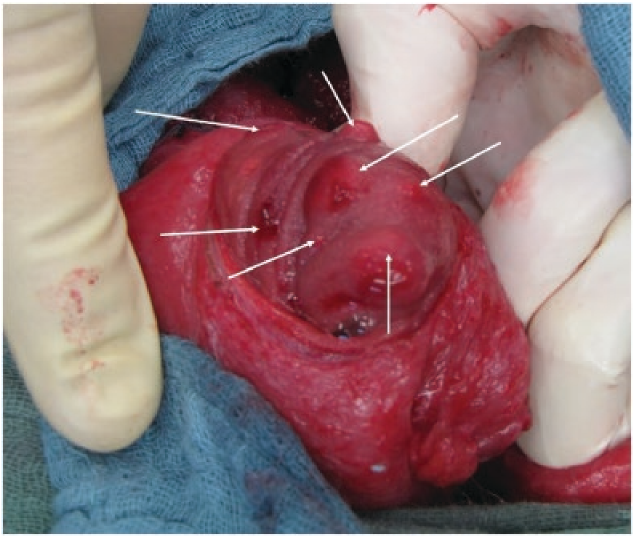

Figure 8 Intraoperative finding of a patient with multiple small intestinal NETs. The numerous tumors are marked with white arrows.

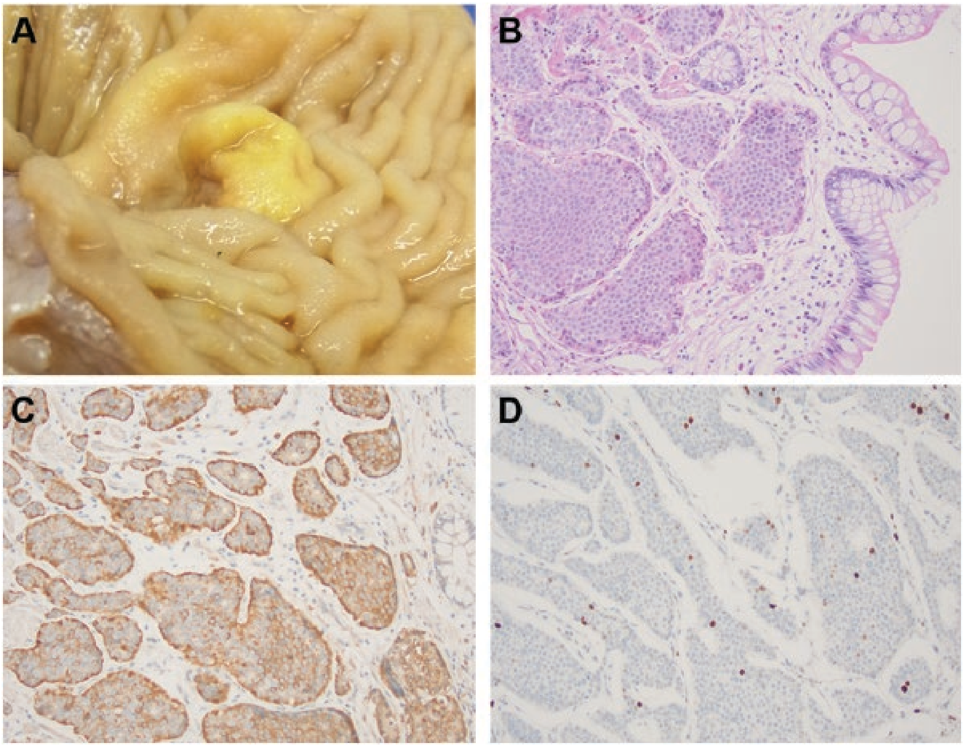

Figure 9 Ileal NET. **A**: Small yellowish polypoid tumor covered by intact mucosa in the ileum. **B**: solid cell nests composed of monomorphic tumor cells in the ileal mucosa (HE, x200). **C**: 1.3 strong expression of serotonin by immunohistochemistry (x200). **D**: Ki67 rate is mostly <4% in ileal NET (x200).

variants/Mb (Banck et al. 2013). The most frequent mutation was detected in the *CDKN1B* gene (encodes p27, a cyclin-dependent kinase inhibitor) in 10% of siNETs (Francis et al. 2013). These mutations are heterozygous truncating mutations without detected second hit. This indicates that *CDKN1B* may be a haploinsufficient tumor suppressor gene; however, no effect of this alteration on other tumor or clinical parameters was demonstrated (Crona et al. 2015). Low-rate mutations were identified in other genes such as *APC* (7.7%), *CDKN2C* (7.7%), *BRAF*, *KRAS*, *PIK3CA*, and *TP53* (3.8% each) (Simbolo et al. 2018), *FGFR2*, *MEN1*, *HOOK3*, *EZH2*, *MLF1*, *CARD11*, *VHL*, *NONO*, and *SMAD1*. Additionally, potentially therapeutically relevant alterations were detected in *SRC*, *AURKA*, *EGFR*, *HSP90*, and *PDGFR* genes. Amplification of *AKT1* and *AKT2* was the most common aberration in PI3K/Akt/ mTOR pathway (Banck et al. 2013). To date, the relevance of these aberrations in the treatment of siNETs remains elusive.

The most common recurrent genetic aberration is the (partial) loss of one copy of chromosome 18, which occurs in 60–78% of the cases (Cunningham et al. 2011; Wang et al. 2005). Due to its high frequency, it has been supposed that the loss of heterozygosity (LOH) of chromosome 18 represents an early event in tumorigenesis. Other chromosomal aberrations such as gains of chromosome 4, 5, 7, 14, and 20 as well as (partial) loss of chromosome 3, 11, and 13 have been reported in siNETs (Nilsson 2013). Gain of chromosome 14 has been shown to be significantly associated with shorter survival (Andersson et al. 2009). Comparative analysis of the different studies led to the proposal of a molecular progression model for siNETs, separating the tumors in two groups. According to this model, most tumors arise from cells which have lost chromosome 18. In a subsequent step, these tumors can also lose (parts) of chromosome 3, 11, or 13 and become metastatic. A smaller group of tumors is characterized by different chromosomal gains (Nilsson 2013).

Karpathakis and colleagues demonstrated a similar classification of siNETs using combined analysis of chromosomal aberrations and methylation profiles. Following this study, about 55% of siNETs harbor chromosome 18 loss only, including all samples with *CDKN1B* mutations. A second group showed no large copy number variations (19%) and third group exhibited numerous copy number variations (26%), e.g. gain of chromosome 4, 5, and 20. In addition, DNA methylation profiles were divergent between these 3 groups. Significantly higher global methylation rate of CpG sites were detected in the second and third group, affecting EGFR, mTOR, and VEGF signaling pathways. In addition, significant differences in progression-free survival (PFS) were observed between these three groups after resection of the primary tumor: the first group had the longest

PFS, followed by the second group with 56 months and by the third group, which showed the most aggressive clinical behavior with 21 months PFS only. Epigenome analysis revealed possible mechanism of metastatic dissemination: promoter hypomethylation, gene body hypermethylation, and increased expression of gastric inhibitory polypeptide receptor gene were associated with the development of liver metastases (Karpathakis et al. 2016). A follow-up study demonstrated that global hypomethylation is enhanced in liver metastases compared with primary siNETs, which was related to increased expression of PI3K, ERBB1, and mTOR signaling pathways (Karpathakis et al. 2017).

Despite frequent losses of chromosome 18, the underlying molecular mechanisms and involved genes remain enigmatic (Nieser et al. 2017). Several candidate tumor suppressor genes are located on chromosome 18, such as *SMAD2, SMAD4, DCC, LAMA3, SERPINB5, RANK/TNFRSF11A*. The latter 3 genes were found to be hypermethylated (Karpathakis et al. 2016) and postulated as epigenetic second hit in siNET following LOH of chromosome 18. Haploinsufficiency of SMAD4 was also proposed as a relevant factor of tumorigenesis in siNETs, that may contribute to metastatic dissemination due to lowered expression of SMAD4 by immunohistochemistry (Hofving et al. 2021). Nevertheless, there is still no unequivocal evidence of recurrent losses of candidate tumor suppressor proteins at protein level.

A recent study identified IGF2 as candidate driver in siNETs in a mouse model that exhibited increased IGF2 mRNA due to loss of imprinting in IGF2 gene (Contractor et al. 2020).

Altogether, despite excellent comprehensive genetic and epigenetic studies, essential mechanisms in tumorigenesis remain to be deciphered in siNETs. Also, pharmacologically addressable novel molecules are still lacking.

References

Andersson, E., Swärd, C., Stenman, G. et al. (2009 Sep). High-resolution genomic profiling reveals gain of chromosome 14 as a predictor of poor outcome in ileal carcinoids. *Endocr Relat Cancer* 16 (3): 953–966.

Anlauf, M., Sipos, B., Boeck, I. et al. (2014). Neuroendocrine neoplasms of the distal jejunum and ileum. *Pathol* 35 (3): 283–293; quiz 294.

Banck, M.S., Kanwar, R., Kulkarni, A.A. et al. (2013). The genomic landscape of small intestine neuroendocrine tumors. *J Clin Invest* 123 (6): 2502–2508.

Chopin-Laly, X., Walter, T., Hervieu, V. et al. (2013). Neuroendocrine neoplasms of the jejunum: a heterogeneous group with distinctive proximal and distal subsets. *Virchows Arch Int J Pathol* 462 (5): 489–499.

Contractor, T., Clausen, R., Harris, G.R. et al. (2020). IGF2 drives formation of ileal neuroendocrine tumors in patients and mice. *Endocr Relat Cancer* 27 (3): 175–186.

Crona, J., Gustavsson, T., Norlén, O. et al. (2015). Somatic mutations and genetic heterogeneity at the CDKN1B locus in small intestinal neuroendocrine tumors. *Ann Surg Oncol* 22 (Suppl 3): S1428–1435.

Cunningham, J.L., Díaz de Ståhl, T., Sjöblom, T. et al. (2011). *Common Pathogenetic Mechanism Involving Human Chromosome 18 in Familial and Sporadic Ileal Carcinoid Tumors. Genes Chromosomes Cancer* 50 (2): 82–94.

Dasari, A., Shen, C., Halperin, D. et al. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 3 (10): 1335–1342.

Ellis, L., Shale, M.J., and Coleman, M.P. (2010). Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol* 105 (12): 2563–2569.

Fraenkel, M., Kim, M., Faggiano, A. et al. (2014). Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocr Relat Cancer* 21 (3): R153–163.

Francis, J.M., Kiezun, A., Ramos, A.H. et al. (2013). Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. *Nat Genet* 45 (12): 1483–1486.

Gangi, A., Siegel, E., Barmparas, G. et al. (2018 Feb). Multifocality in Small Bowel Neuroendocrine Tumors. *J Gastrointest Surg Off J Soc Surg Aliment Tract* 22 (2): 303–309.

Hofving, T., Elias, E., Rehammar, A. et al. (2021). SMAD4 haploinsufficiency in small intestinal neuroendocrine tumors. *BMC Cancer* 21 (1): 101.

Hoskoppal, D., Epstein, J.I., Gown, A.M. et al. (2020). SATB2 protein expression by immunohistochemistry is a sensitive and specific marker of appendiceal and rectosigmoid well differentiated neuroendocrine tumours. *Histopathology* 76 (4): 550–559.

Jaffee, I.M., Rahmani, M., Singhal, M.G., and Younes, M. (2006). Expression of the intestinal transcription factor CDX2 in carcinoid tumors is a marker of midgut origin. *Arch Pathol Lab Med* 130 (10): 1522–1526.

Jann, H., Roll, S., Couvelard, A. et al. (2011). Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer* 117 (15): 3332–3341.

Karpathakis, A., Dibra, H., Pipinikas, C. et al. (2016). Prognostic impact of novel molecular subtypes of small intestinal neuroendocrine tumor. *Clin Cancer Res Off J Am Assoc Cancer Res* 22 (1): 250–258.

Karpathakis, A., Dibra, H., Pipinikas, C. et al. (2017). Progressive epigenetic dysregulation in neuroendocrine tumour liver metastases. *Endocr Relat Cancer* 24 (2): L21–5.

Lawrence, B., Gustafsson, B.I., Chan, A. et al. (2011). The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 40 (1): 1–18, VII.

Mai, R., Kaemmerer, D., Träger, T. et al. (2019). Different somatostatin and CXCR4 chemokine receptor expression in gastroenteropancreatic neuroendocrine neoplasms depending on their origin. *Sci Rep* 9 (1): 4339.

McHugh, K.E., Mukhopadhyay, S., Doxtader, E.E. et al. (2020). INSM1 Is a highly specific marker of neuroendocrine differentiation in primary neoplasms of the gastrointestinal tract, appendix, and pancreas. *Am J Clin Pathol* 153 (6): 811–820.

Nieser, M., Henopp, T., Brix, J. et al. (2017). loss of chromosome 18 in neuroendocrine tumors of the small intestine: the enigma remains. *Neuroendocrinology* 104 (3): 302–312.

Nilsson, O. (2013). Profiling of ileal carcinoids. *Neuroendocrinology* 97 (1): 7–18.

Perez, K., Kulke, M.H., Chittenden, A. et al. (2021). Clinical implications of pathogenic germline variants in small intestine neuroendocrine tumors (SI-NETs). *JCO Precis Oncol* 5: 808–816.

Schmitt, A.M., Riniker, F., Anlauf, M. et al. (2008). Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. *Am J Surg Pathol* 32 (3): 420–425.

Simbolo, M., Vicentini, C., Mafficini, A. et al. (2018). Mutational and copy number asset of primary sporadic neuroendocrine tumors of the small intestine. *Virchows Arch Int J Pathol* 473 (6): 709–717.

Wang, G.G., Yao, J.C., Worah, S. et al. (2005). Comparison of genetic alterations in neuroendocrine tumors: frequent loss of chromosome 18 in ileal carcinoid tumors. *Mod Pathol Off J U S Can Acad Pathol Inc* 18 (8): 1079–1087.

Appendix

Inga Boeck & Martin Anlauf

Epidemiology and Pathology

Epidemiology

Appendiceal neuroendocrine neoplasms (ANENs) represent frequent neoplasms with an estimated annual incidence of 0.15–0.6/100,000 (Alkhayyat et al. 2021; Pape et al. 2016). The appendix is one of the most frequent sites for gastroenteropancreatic NENs (GEP-NENs) according to epidemiological studies and NEN are found in one out of 200 appendectomies (Alexandraki et al. 2016; Dasari et al. 2017; Diets et al. 2017; Gouffon et al. 2014; Landry et al. 2008; Niederle et al. 2010). In pediatric populations, ANENs comprise the first or second most common GEP-NENs (Alexandraki et al. 2016; Diets et al. 2017; Scott and Upadhyay 2011). In oncological NEN cohorts, the appendix accounts only for 3.1% of primary tumors (German NET Registry 2018). Neuroendocrine tumors (NETs) are the most common neoplasms of the appendix (Alkhayyat et al. 2021) and amount to 43–57% of the primary tumors of the appendix (Alexandraki et al. 2016). NETs are the reason for 0.16–2.3% of all appendectomies (Alexandraki et al. 2016). Their prevalence decreased over time (McCusker et al. 2002; McGory et al. 2005; Niederle et al. 2010). ANENs are mostly found incidentally in both adults and children in connection with an appendicitis or other abdominal illnesses (Alexandraki et al. 2016; Pape et al. 2016). In contrast to other appendiceal tumors and NENs in any other site, patients with appendiceal NETs are significantly younger (median 38 years) (Alexandraki et al. 2016; Niederle et al. 2010, Quaedvlieg et al. 200). Mean age at diagnosis ranges between 38 and 51 years (Garcia-Carbonero et al. 2010; Ploeckinger et al. 2009). However, appendiceal NENs have also been reported in pediatric patients between 4.5 and 19.5 years (Kulkarni and Sergi 2013, Scott and Upadhyay 2011). The appendix is the organ with the highest rate of NET G1 tumors, followed by duodenum, rectum, and stomach. Thus, early tumor stages prevail, which rarely reach clinical significance and are classified as benign (German NET Registry & Collaborators 2018; Niederle et al. 2010). There appears to be a slight female predominance for ANENs (Pape et al. 2016). Racial differences may occur (Pape et al. 2016; Quaedvlieg et al. 2001). Malignant tumors appear to occur more often in Caucasians compared to other ethnicities (Pape et al. 2016).

Pathology

Appendiceal NETs typically arise in the tip of the appendix (Assarzadegan and Montgomery 2021). Macroscopically, these neoplasms appear as yellowish, well-demarcated nodules. Appendiceal NETs consist of uniform polygonal tumor cells, frequently arranged in large nests (Tomioka et al. 2013) showing peripheral palisading and glandular formations. Appendiceal neuroendocrine carcinomas (NECs) are exceedingly rare (Pape et al. 2016) with only one case being published to date that meets the 2010 diagnostic criteria of the World Health Organization (Tomioka et al. 2013). Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) of the appendix are rare and can display a combination of a NEC and an adenocarcinoma. Goblet cell adenocarcinoma is now regarded as an adenocarcinoma subtype rather than a neuroendocrine neoplasm and staged accordingly (Assarzadegan and Montgomery 2021; WHO 2019).

The histopathological characterization demands immunohistochemical proof of the neuroendocrine entity by staining for specific neuroendocrine markers synaptophysin and Chromogranin A (CgA) (Moris et al. 2018). NETs can consist of two major cell types: the enterochromaffin (EC)-cell type produces serotonin, whereas the L-cell type produces GLP-1 or other proglucagon-derived peptides (Volante et al. 2021). Proliferative capacity determines tumor grading according to the current WHO classification (Table 6) (Rindi et al. 2007; WHO Classification of Tumours Editorial Board 2019). NENs of the appendix are usually G1 or G2 (Ki-67 index <20%) and thus should be considered NET (Pape et al. 2016). It is suggested that G2 NENs carry a higher risk for relapse and metastasis (Moris et al. 2018; Volante et al. 2013). Table 6 summarizes the prognostic factors of ANENs.

Besides WHO grading, TNM staging according to either the UICC/AJCC classification or ENETS guidelines (or according

Table 6 Prognostic factors of appendiceal neuroendocrine neoplasms.

Tumor characteristic	Comment
1. Size	
<1 cm	Most common; 100% survival post-appendectomy
1–2 cm	5–25% of cases, if >1.5 cm can be accompanied by lymph node metastasis
>2 cm	<10% of cases, up to 40% risk for systemic dissemination
2. Location	
Tip	60–75%
Body	5–20%
Base	<10%, higher risk for R1- or R2 resection status
3. Mesoappendiceal invasion	Higher risk of V1 or L1, aggressive behavior
>3 mm	

Adapted from Moris et al. (2018).

Table 7 TNM staging for appendiceal NEN according to ENETS guidelines and UICC/AJCC classification.

	ENETS guidelines	UICC/AJCC classification
T-primary tumour		
X	Primary tumour not assessed/ assessable	
0	No evidence of primary tumour	
1	Tumour ≤ 1 cm with infiltration of the submucosa and muscularis propria	
1a		Tumour ≤ 1 cm
1b		Tumour > 1 cm but ≤ 2 cm
2	Tumour ≤ 2 cm with infiltration of the submucosa, muscularis propria and/ or minimal (≤ 3 mm) infiltration of the subserosa and/ or mesoappendix	Tumour > 2 cm but ≤ 4 cm or with extension into the caecum
3	Tumour > 2 cm and / or extensive (>3 mm) infiltration of the subserosa and/ or mesoappendix	Tumour > 4 cm or with extension into the ileum
4	Tumour with infiltration of the peritoneum and/ or other neighbouring organs	Tumour with perforation of the peritoneum or invasion of other adjacent structures
N – regional lymph node metastasis		
NX	Regional lymph nodes not assessed / assessable No regional lymph node metastasis Locoregional lymph node metastasis/-es	
N0		
N1		
M – distant metastasis		
MX	Distant metastasis not assessed/assessable No distant metastasis Distant metastasis/-es	

to both, Table 7) is recommended (Pape et al. 2016; Rindi et al. 2007; Washington et al. 2010; WHO Classification of Tumours Editorial Board 2019). No genetic association has been recorded, so there is no need for genetic testing (Pape et al. 2016). Single cases of NETs show more than one mutation involving *TP53*, *PTEN*, *SMAD4*, and *EGFR* (Park et al. 2019).

Clinical Presentation and Diagnosis

Matthias Schott

Symptoms and Clinical Signs

Endocrine midgut tumors can be divided according to their clinical behavior into functioning and nonfunctioning tumors; the latter constitute about 90% of the tumors (Capella et al. 1994). The functioning tumors are responsible for the carcinoid syndrome. Most endocrine midgut tumors are well-differentiated and slow growing, whereas a minority have a more aggressive course (Kaltsas et al. 2004).

Carcinoid syndrome occurs in 20–30% of patients with midgut carcinoid tumors and approximately 5% of bronchial carcinoids. Other foregut tumors can cause carcinoid syndrome although this is uncommon (1%). Carcinoid syndrome is usually seen in patients with liver metastases (in 95% patients), but excess tachykinins, serotonin production from retroperitoneal metastases, or ovarian tumors can bypass the liver to cause the syndrome (Robertson et al. 2006).

Patients often describe having symptoms for many months prior to presentation. The two most common symptoms are diarrhea and flushing, while wheeze occurs less commonly. Often diarrhea is associated with crampy abdominal pain and urgency and can occur during both day and night. Flushing is characteristically described as a sudden onset of pink to red discoloration involving the face and upper trunk. This usually lasts a few minutes and can occur intermittently throughout the day. Triggers leading to flushing and diarrhea include stress, tyramine containing foods (chocolate, bananas, walnuts), and alcohol. In patients with atypical flushing, which may last for several hours, telangiectasia and hypertrophy of the face may be seen. Wheeze is caused by bronchial constriction mediated via tachykinins and bradykinins and is more common in patients with bronchial carcinoid tumors. A raised jugular venous pressure and features of right heart failure may be present in patients with carcinoid heart disease related to carcinoid syndrome. Right-sided cardiac murmurs of tricuspid regurgitation and pulmonary stenosis may be heard on cardiovascular examination. Other hormone-related manifestations include morphea and pellagra-type rash if nicotinic acid deficiency has been induced. With severe, long-standing hepatomegaly of local infiltration, inferior vena cava obstruction, or even lymphangiectasia leading to ascites may occur.

The prognosis of patients with carcinoid syndrome varies widely and although some patients may have rapidly progressive disease, in others survival of decades may occur.

Appendiceal NENs in adults as well as in children are mostly incidental findings in post-appendicectomy specimen and therefore no characteristic tumor-specific symptomatology has been established. However, symptoms that lead to appendectomy such as right lower abdominal pain are indirectly associated with appendiceal NENs, although, due to their most frequent localization at the tip of the appendix (approx. 70%), these tumors are very likely not causative of acute appendicitis. In the rare cases of distant metastases, these may cause symptoms related to the localization of the metastases. A carcinoid syndrome is an extreme exception in metastatic patients and more likely associated with an intestinal primary tumor (Hrabe 2020).

Diagnosis

Diagnosis of siNETs requires biochemical and topographical imaging. Patients with suspected small intestine NETs should undergo biochemical testing. Patients with NETs of the midgut have increased serotonin production, and elevated serotonin levels can be measured directly in the plasma or indirectly via the serotonin metabolite, 5-HIAA, in the urine (Feldman and O'Dorisio 1986). Elevated 24-hour urinary 5-HIAA levels have a sensitivity of 73% and a specificity of 100% in predicting the presence of a NET in the midgut area (Ardill and Erikkson 2003; Feldman and O'Dorisio 1986). Collection of urine should be performed during diet restriction (bananas, chocolate, tea, coffee, walnuts, and spicy food should be avoided). Usually the mean of two 24-hour collections is estimated.

Plasma chromogranin A is increased in 87% of patients with midgut NETs (Janson et al. 1997). It also appears to correlate with tumor burden and can therefore be used to predict prognosis, particularly in classic midgut NETs (Janson et al. 1997). This relationship is attested by a postresection study in which the presence of mesenteric lymph node metastases was associated with chromogranin A elevation in all 25 patients, whereas only three had elevation of 5-HIAA (Eriksson and Oberg 1991). Elevation of chromogranin A can precede often radiologic evidence of a recurrence in different types of NETs. If chromogranin A and urinary 5-HIAA are normal, but a midgut carcinoid is strongly suspected, a provocative test with pentagastrin measuring the tachykinin, neuropeptide K (NPK), can be performed (Modlin and Tang 1997). False positive elevation of chromogranin A can be seen in renal impairment, liver failure, atrophic gastritis, and inflammatory bowel disease (Granberg et al. 1999).

Diagnostic Imaging

Clarisse Dromain & Nicolas Villard

Jejunum and Ileum

Primary NENs of the small bowel are usually small and difficult to diagnose. CT enteroclysis is the imaging of reference for small bowel primary tumor detection. Indeed, since most of these tumors are small (<2 cm), conventional CT is most often negative for the primary tumor. By combining small bowel distension and intra-luminal low-contrast, CT enteroclysis maximize contrast between the lumen and small bowel wall, thus facilitating the assessment of the small bowel wall. CT enteroclysis has been shown to bear 100% sensitivity and 96% specificity in identifying small bowel NENs (Kamaoui et al. 2010).

Imaging features of small bowel NENs in CT enteroclysis are a focal nodular mass located in the small bowel wall or an intraluminal polypoid mass showing marked enhancement after injection (Kamaoui et al. 2010). The median size of lesion is 14 mm, ranging from 5 to 30 mm. Most of lesions are located in the terminal part of the ileum. Digestive NENs are multifocal in 30% but often underestimated during the initial work-up.

Other very common associated imaging features are a mesenteric fibrotic mass, small bowel ischemia, and enlargement of mesenteric lymph nodes. CT detection of a mesenteric mass might be the first clue suggesting the need to search for a primary tumor within the small bowel. Mesenteric fibrotic mass appears on CT images as a 3 cm (median size) round or oval well-defined soft-tissue mass, with radiating linear strands with stellate or spoke-wheel configuration, and thickened adjacent bowel loops (Pantongrag-Brown et al. 1995). Small, stippled, or coarse calcifications are presents in 70% of cases.

The linear radiating strands observed in the mesentery on CT scans are largely due to the fibrotic process. Moreover, it has been found that the degree of histologic fibrosis tended to be directly related to the degree of radiating strands detected by CT scans (Pantongrag-Brown et al. 1995). This profound desmoplastic response is caused by hormonally active substances, especially serotonin, secreted by carcinoid tumors. The same hormones also provoked desmoplastic effects within the bowel wall.

Small bowel wall thickening observed on CT images is the result of fibrosis within the bowel wall and edema due to mesenteric ischemia. Mesenteric ischemia is a result of obstruction of the mesenteric artery due to infiltrated paraaortic lymph nodes or more often the development of elastic mesenteric vascular sclerosis induced by tumor-produced hormones and in particular by the release of vasoconstrictive substances (Sworn et al. 1978). These elastic mesenteric vascular changes are only noted in cases in which there is spread of tumor in the mesentery, suggesting that this vascular lesion may be caused by the local effect of substances secreted by the tumor. Imaging features of small bowel ischemia include bowel wall thickening, dilatation of bowel lumen, and with sometimes a halo target appearance representing hyperemia and hyperperfusion associated with surrounding mural edema.

Appendix

Due to the small size of tumor and the high rate of motion artifacts in the area of pelvic fossa, multiphasic CT with arterial and portal phase is the imaging of reference for the diagnosis and the staging of NENs of the appendix.

When visible on images, NENs of the appendix may display two different patterns. The first is an appendicitis pattern with a diffuse thickening of the appendix with peri-appendiceal fat stranding. The second pattern, more suggestive of a NEN, is a soft-tissue hyperenhancing mass located in the tip of the appendix (Ganeshan et al. 2013).

Surgical Treatment

Levent Dizdar & Wolfram Trudo Knoefel

Jejunum and Ileum

Preoperative Assessment

All patients with small bowel NENs (siNENs) localized in the ileum and jejunum should be evaluated for potentially curative surgery by a multidisciplinary team. For accurate indication and surgical planning, staging by computed tomography and somatostatin receptor imaging (somatostatin receptor scintigraphy (SRS) or positron emission tomography (PET) scanning with ^{68}Gallium) should be performed preoperatively (Lardiere-Deguelte et al. 2016; Niederle et al. 2016; Partelli et al. 2017). In addition, current guidelines recommend determination of 5-hydroxyindoleacetic acid (5-HIAA) in 24-hour urine and echocardiography before surgery to rule out carcinoid syndrome and carcinoid heart disease (Partelli et al. 2017). If a patient is diagnosed with carcinoid syndrome preoperatively, somatostatin analogues (SSAs) should be administered perioperatively to prevent carcinoid crisis. Given the association of siNENs with other colorectal neoplasms, preoperative colonoscopy appears reasonable (Prommegger et al. 2004).

Indication for Surgery

In general, surgical resection of siNETs is the treatment of choice for curative intent. Since half of all siNETs < 1 cm already harbor lymph node metastases, even small and incidentally discovered tumors require radical surgical resection with lymphadenectomy (Partelli et al. 2017; Walsh et al. 2016). Systematic lymphadenectomy with resection of at least 8 lymph nodes should always be performed, as this procedure is associated with a significant improvement in survival (Landry et al. 2013; Partelli et al. 2017). In addition, because siNETs often occur multifocally (approximately 20–30% of cases), complete bimanual palpation of the entire jejunum and ileum from the ligament of Treitz to the ileo-cecal valve should be performed as part of any surgical procedure (Chambers et al. 2008; Partelli et al. 2017). Patients with locally advanced siNETs with extensive mesenteric tumor manifestations should be operated in experienced centers. With appropriate surgical expertise, a complete tumor resection can be achieved in approximately 80% of the cases with advanced disease (Partelli et al. 2017; Pasquer et al. 2015). Small intestinal NETs should be considered unresectable if mesenteric tumor deposits entirely surround the mesenteric vessel root or extend retroperitoneally (Partelli et al. 2017). However, even in patients who are classified as unresectable, palliative surgical resections are indicated if symptoms such as chronic bowel obstruction or localized intestinal ischemia occur, as these surgical measures can lead to significant improvement in symptoms and survival (Chambers et al. 2008; Partelli et al. 2017). For resectable liver metastases, radical resection of the primary tumor and metastases is recommended in patients with well-differentiated G1 and G2 tumors (Partelli et al. 2017). In cases of unresectable distant metastasis and symptomatic siNETs (ileus, hemorrhage, mesenteric ischemia), the primary tumor and lymph node metastases should be removed to improve quality of life and prevent clinical deterioration or death. In addition, primary tumor resection may also be considered in asymptomatic siNET patients with unresectable hepatic metastases to prevent complications and improve patient prognosis (Ahmed et al. 2009; Givi et al. 2006).

Surgical Approach

Surgical treatment of siNETs should include complete oncologic resection of the primary tumor as well as regional lymph nodes and mesenteric fibrosis, if possible. The resection should be performed with meticulous attention in order to preserve the proximal superior mesenteric artery (SMA) and vein (SMV) and maximize the length of the remaining viable intestine. In ileal NET, an attempt to perform oncologic resection of the affected segment should be made in order to preserve the ileocecal valve and thus reduce the risk of diarrhea. However, in cases located near the ascending colon, a right hemicolectomy must be performed for oncologic reasons (Habbe et al. 2013). Regional lymphadenectomy should include all lymph nodes of the affected intestinal segment up to the origin of the segmental vascular branches from the SMA and SMV and include at least 8 lymph nodes (Landry et al. 2013; Partelli et al. 2017; Pasquer et al. 2015). Abdominal lymph nodes outside the superior mesenteric vessels should be resected only if metastasis is suspected (Howe et al. 2017). To accurately determine the extent of the disease, intraoperative staging must always be performed. In particular, a careful exploration of the entire intestine including the mesentery, the pelvis, the diaphragm, and the liver including intraoperative liver sonography should be performed (Howe et al. 2017). If further tumor manifestations are detected during surgery, the procedure should be extended to include a resection of additional intestinal tumors and hepatic, ovarian, or peritoneal metastases, if possible. For the treatment of peritoneal metastases of siNETs, there is no evidence supporting the use of hyperthermic intraperitoneal chemotherapy (HIPEC) as an adjunct to local resection to date (Howe et al. 2017). In current guidelines for the treatment of siNETs, open exploratory laparotomy with careful palpation of the entire small bowel is considered the gold standard. Minimally invasive surgery is not recommended, particularly due to the often small size and multifocal nature of siNETs (Howe et al. 2017; Niederle et al. 2016; Partelli et al. 2017).

Prophylactic Cholecystectomy

If long-term SSA therapy is highly likely, prophylactic cholecystectomy may be appropriate as part of the initial tumor resection because SSA therapy is associated with a high risk of gallstone formation and prior abdominal procedures may complicate future laparoscopic cholecystectomy (Habbe et al. 2013). However, the benefit of this approach has not been proven so far, so that the advantages and disadvantages of cholecystectomy should be considered individually by the operating surgeon depending on technical and clinical aspects (e.g., previous cholecystitis or cholangitis, planned TACE or SIRT, risk of cholecystectomy in an emergency situation).

Appendix

Appendiceal NETs are often discovered incidentally during abdominal surgery for suspected or manifest acute appendicitis. In such cases, the tumor can already be identified intraoperatively or even only in the course of the histopathological examination. Surgery represents the mainstay of treatment for local or loco-regional appendiceal NETs, with simple appendectomy or oncologic right-sided hemicolectomy with lymphadenectomy (Boudreaux et al. 2010; Pape et al. 2016, 2012). Well-differentiated G1 and G2 NETs of the appendix that are smaller than 1 cm and have been completely resected (R0) do not require further therapy. The only exceptions in which a right-sided hemicolectomy may be justified in this constellation are NETs localized at the base of the appendix or when a mesoappendiceal invasion > 3 mm is detected histopathologically (Pape et al. 2016). In appendiceal NETs with a size > 1 cm but < 2 cm, lymph node and distant metastases also occur rarely but have been reported repeatedly. In these cases, risk factors such as grading (G2), angio- (V1) or lymphangio- (L1) invasion, and mesoappendiceal infiltration > 3 mm should guide the recommendation regarding the indication for right-sided hemicolectomy with lymph node dissection (Pape et al. 2016). Accordingly, the Nordic guidelines, for example, recommend right oncologic hemicolectomy for appendiceal NETs with a size of 1–2 cm when at least two of the previously mentioned risk factors are present (Janson et al. 2021). A recent retrospective, pooled cohort study from Europe has shown that a right-sided hemicolectomy is not indicated after complete resection of 1-2 cm appendiceal NET, even if risk factors are present (Nesti et al. 2023). NETs of the appendix larger than 2 cm, as well as G3 NETs or NECs of any size, should always be treated with oncologic right hemicolectomy due to the high risk of lymph node metastasis or local recurrence during the course of the disease (Boudreaux et al. 2010; Janson et al. 2021; Pape et al. 2016, 2012). Moreover, in patients who have undergone incomplete tumor resection (R1) or already exhibit lymph node metastases, a right hemicolectomy should be performed regardless of the tumor size (Janson et al. 2021).

Goblet Cell Adenocarcinoma (GCAC) of the Appendix

These neoplasms often exhibit neuroendocrine differentiation; however, they are not considered part of the digestive system NENs according to most recent classifications and will be only addressed briefly. Due to the high risk of metastasis as well as the unfavorable prognosis, oncologic right-sided hemicolectomy should be performed if goblet cell adenocarcinoma (GCAC) of the appendix is detected (Pape et al. 2012). Bilateral salpingo-ophrectomy in female patients with GCAC has been suggested in some reports but its prognostic benefit remains unproven so far (Pahlavan and Kanthan 2005; Pape et al. 2012). In cases with extensive peritoneal involvement, the use of HIPEC is recommended in some studies after complete or near-complete cytoreductive surgery. However, the prognostic benefit of this approach has not been proven yet (Lamarca et al. 2016; Pahlavan and Kanthan 2005; Pape et al. 2012; Rossi et al. 2015). The surgical treatment of liver metastases from GCAC of the appendix should follow the treatment recommendations for colorectal adenocarcinoma (Pape et al. 2012).

References

Ahmed, A., Turner, G., King, B. et al. (2009). Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer* 16 (3): 885–894.

Alexandraki, K.I., Kaltsas, G.A., Grozinsky-Glasberg, S. et al. (2016). Appendiceal neuroendocrine neoplasms: diagnosis and management. *Endocr Relat Cancer* 23 (1): R27–41.

Alkhayyat, M., Saleh, M.A., Coronado, W. et al. (2021). Epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019). *Ann Gastroenterol* 34 (5): 713–720.

Ardill, J.E. and Erikkson, B. (2003 Dec). The importance of the measurement of circulating markers in patients with neuroendocrine tumours of the pancreas and gut. *Endocr Relat Cancer* 10 (4): 459–462.

Assarzadegan, N. and Montgomery, E. (2021). What is new in the 2019 World Health Organization (WHO) classification of tumors of the digestive system: review of selected updates on neuroendocrine neoplasms, appendiceal tumors, and molecular testing. *Arch Pathol Lab Med* 145 (6): 664–677.

Boudreaux, J.P., Klimstra, D.S., Hassan, M.M. et al. (2010). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas* 39 (6): 753–766.

Capella, C., Heitz, P.U., Höfler, H. et al. (1994). Revised classification of neuroendocrine tumors of the lung, pancreas and gut. *Digestion* 55 (Suppl 3): 11–23.

Chambers, A.J., Pasieka, J.L., Dixon, E., and Rorstad, O. (2008). The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors. *Surgery* 144 (4): 645–651; discussion 51-3.

Dasari, A., Shen, C., Halperin, D. et al. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 3 (10): 1335–1342.

Diets, I.J., Nagtegaal, I.D., Loeffen, J. et al. (2017). Childhood neuroendocrine tumours: a descriptive study revealing clues for genetic predisposition. *Br J Cancer* 116 (2): 163–168. 17.

Eriksson, B. and Oberg, K. (1991). Peptide hormones as tumor markers in neuroendocrine gastrointestinal tumors. *Acta Oncol* 30 (4): 477–483.

Feldman, J.M. and O'Dorisio, T.M. (1986). Role of neuropeptides and serotonin in the diagnosis of carcinoid tumors. *Am J Med* 81 (6B): 41–48.

Ganeshan, D., Bhosale, P., Yang, T., and Kundra, V. (2013). Imaging features of carcinoid tumors of the gastrointestinal tract. *Am J Roentgenol* 201 (4): 773–786.

Garcia-Carbonero, R., Capdevila, J., Crespo-Herrero, G. et al. (2010). Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol Off J Eur Soc Med Oncol* 21 (9): 1794–1803.

German NET Registry & Collaborators. (2018). Neuroendokrine Neoplasien im deutschen NET-Register. *Z Fuer Gastroenterol* 56 (10): 1237–1246.

Givi, B., Pommier, S.J., Thompson, A.K. et al. (2006). Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. *Surgery* 140 (6): 891–897; discussion 7-8.

Gouffon, M., Iff, S., Ziegler, K. et al. (2014 Feb 19). Diagnosis and workup of 522 consecutive patients with neuroendocrine neoplasms in Switzerland. *Swiss Med Wkly* [Internet]. available at: http://doi.emh.ch/smw.2014.13924 (accessed 26th March 2022).

Granberg, D., Stridsberg, M., Seensalu, R. et al. (1999). Plasma chromogranin A in patients with multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 84 (8): 2712–2717.

Habbe, N., Fendrich, V., Heverhagen, A. et al. (2013). Outcome of surgery for ileojejunal neuroendocrine tumors. *Surg Today* 43 (10): 1168–1174.

Howe, J.R., Cardona, K., Fraker, D.L. et al. (2017). The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the North American Neuroendocrine Tumor Society. *Pancreas* 46 (6): 715–731.

Hrabe, J. (2020). Neuroendocrine tumors of the appendix, colon, and rectum. *Surg Oncol Clin N Am* 29 (2): 267–279.

Janson, E.T., Holmberg, L., Stridsberg, M. et al. (1997). Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. *Ann Oncol* 8 (7): 685–690.

Janson, E.T., Knigge, U., Dam, G. et al. (2021). Nordic guidelines 2021 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncol* 60 (7): 931–941.

Kaltsas, G.A., Besser, G.M., and Grossman, A.B. (2004). The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev* 25 (3): 458–511.

Kamaoui, I., De-Luca, V., Ficarelli, S. et al. (2010). Value of CT enteroclysis in suspected small-bowel carcinoid tumors. *Am J Roentgenol* 194 (3): 629–633.

Kulkarni, K.P. and Sergi, C. (2013). Appendix carcinoids in childhood: long-term experience at a single institution in Western Canada and systematic review. *Pediatr Int Off J Jpn Pediatr Soc* 55 (2): 157–162.

Lamarca, A., Nonaka, D., Lopez Escola, C. et al. (2016). Appendiceal goblet cell carcinoids: management considerations from a reference peritoneal tumour service centre and ENETS centre of excellence. *Neuroendocrinology* 103 (5): 500–517.

Landry, C.S., Lin, H.Y., Phan, A. et al. (2013). Resection of at-risk mesenteric lymph nodes is associated with improved survival in patients with small bowel neuroendocrine tumors. *World J Surg* 37 (7): 1695–1700.

Landry, C.S., Woodall, C., Scoggins, C.R. et al. (2008). Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. *Arch Surg Chic Ill 1960* 143 (7): 664–670; discussion 670.

Lardiere-Deguelte, S., de Mestier, L., Appere, F. et al. (2016). toward a preoperative classification of lymph node metastases in patients with small intestinal neuroendocrine tumors in the era of intestinal-sparing surgery. *Neuroendocrinology* 103 (5): 552–559.

McCusker, M.E., Coté, T.R., Clegg, L.X., and Sobin, L.H. (2002). Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. *Cancer* 94 (12): 3307–3312.

McGory, M.L., Maggard, M.A., Kang, H. et al. (2005). Malignancies of the appendix: beyond case series reports. *Dis Colon Rectum* 48 (12): 2264–2271.

Modlin, I.M. and Tang, L.H. (1997). Approaches to the diagnosis of gut neuroendocrine tumors: the last word (today). *Gastroenterology* 112 (2): 583–590.

Moris, D., Tsilimigras, D.I., Vagios, S. et al. (2018). Neuroendocrine neoplasms of the appendix: a review of the literature. *Anticancer Res* 38 (2): 601–611.

Nesti, C., Bräutigam, K., Benavent, M. et al. (2023). Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: a retrospective, Europe-wide, pooled cohort study. *Lancet Oncol* 24 (2): 187–194.

Niederle, B., Pape, U.F., Costa, F. et al. (2016). ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology* 103 (2): 125–138.

Niederle, M.B., Hackl, M., Kaserer, K., and Niederle, B. (2010). Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 17 (4): 909–918.

Pahlavan, P.S. and Kanthan, R. (2005). Goblet cell carcinoid of the appendix. *World J Surg Oncol* 3: 36.

Pantongrag-Brown, L., Buetow, P.C., Carr, N.J. et al. (1995). Calcification and fibrosis in mesenteric carcinoid tumor: CT findings and pathologic correlation. *Am J Roentgenol* 164 (2): 387–391.

Pape, U.-F., Niederle, B., Costa, F. et al. (2016). ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). *Neuroendocrinology* 103 (2): 144–152.

Pape, U.F., Perren, A., Niederle, B. et al. (2012). ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology* 95 (2): 135–156.

Park, H.Y., Kwon, M.J., Kang, H.S. et al. (2019). Targeted next-generation sequencing of well-differentiated rectal, gastric, and appendiceal neuroendocrine tumors to identify potential targets. *Hum Pathol* 87: 83–94.

Partelli, S., Bartsch, D.K., Capdevila, J. et al. (2017). ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology* 105 (3): 255–265.

Pasquer, A., Walter, T., Hervieu, V. et al. (2015). Surgical management of small bowel neuroendocrine tumors: specific requirements and their impact on staging and prognosis. *Ann Surg Oncol* 22 (Suppl 3): S742–9.

Ploeckinger, U., Kloeppel, G., Wiedenmann, B., and Lohmann, R., representatives of 21 German NET Centers (2009). The German NET-registry: an audit on the diagnosis and therapy of neuroendocrine tumors. *Neuroendocrinology* 90 (4): 349–363.

Prommegger, R., Ensinger, C., Steiner, P. et al. (2004). Neuroendocrine tumors and second primary malignancy–a relationship with clinical impact? *Anticancer Res* 24 (2C): 1049–1051.

Quaedvlieg, P.F., Visser, O., Lamers, C.B. et al. (2001). Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann Oncol Off J Eur Soc Med Oncol* 12 (9): 1295–1300.

Rindi, G., Klöppel, G., Couvelard, A. et al. (2007). TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch Int J Pathol* 451 (4): 757–762.

Robertson, R.G., Geiger, W.J., and Davis, N.B. (2006). Carcinoid tumors. *Am Fam Physician* 74 (3): 429–434.

Rossi, R.E., Luong, T.V., Caplin, M.E. et al. (2015). Goblet cell appendiceal tumors–management dilemmas and long-term outcomes. *Surg Oncol* 24 (1): 47–53.

Scott, A. and Upadhyay, V. (2011 25 März). Carcinoid tumours of the appendix in children in Auckland, New Zealand: 1965-2008. *N Z Med J* 124 (1331): 56–60.

Sworn, M.J., Reasbeck, P., and Buchanan, R. (1978). Intestinal ischaemia associated with ileal carcinoid tumours. *Br J Surg* 65 (5): 313–315.

Tomioka, K., Fukoe, Y., Lee, Y. et al. (2013). Primary neuroendocrine carcinoma of the appendix: a case report and review of the literature. *Anticancer Res* 33 (6): 2635–2638.

Volante, M., Daniele, L., Asioli, S. et al. (2013). Tumor staging but not grading is associated with adverse clinical outcome in neuroendocrine tumors of the appendix: a retrospective clinical pathologic analysis of 138 cases. *Am J Surg Pathol* 37 (4): 606–612.

Volante, M., Grillo, F., Massa, F. et al. (2021). Neuroendocrine neoplasms of the appendix, colon and rectum. *Pathologica* 113 (1): 19–27.

Walsh, J.C., Schaeffer, D.F., Kirsch, R. et al. (2016). Ileal "carcinoid" tumors-small size belies deadly intent: high rate of nodal metastasis in tumors </=1 cm in size. *Hum Pathol* 56: 123–127.

Washington, M.K., Tang, L.H., Berlin, J. et al. (2010). Protocol for the examination of specimens from patients with neuroendocrine tumors (carcinoid tumors) of the appendix. *Arch Pathol Lab Med* 134 (2): 171–175.

WHO Classification of Tumours Editorial Board. (2019). *Digestive System Tumours*, 5e. Lyon: International Agency for Research on Cancer (IARC).

Colon and Rectum

Epidemiology and Pathology

Björn Konukiewitz & Moritz Jesinghaus

Epidemiology

The reported annual incidence of colorectal NENs is about 1.4 cases per 100,000 persons in the United States. NECs and MiNEN are found in all regions of the colorectum, whereas NETs mainly occur in the rectum. Colorectal NENs arise in the sixth and seventh decade and show a discrete male predominance. The prognosis of colorectal NEN is highly variable and depends on the tumor type (Dasari et al. 2017; WHO 2019).

Pathology

Similarly to other GEP-NENs, colorectal NENs are classified according to the WHO classification of the digestive system, into well-differentiated NEN (Neuroendocrine Tumor; NET), poorly differentiated NEN (Neuroendocrine Carcinoma; NEC), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN), which are mostly mixed neuroendocrine-non-neuroendocrine carcinomas (MANEC). Furthermore, NETs are subclassified into G1, G2, and G3 tumors based on their proliferative activity (Ki-67 index and mitosis). Colorectal NENs show strong site-specific differences as NETs occur almost exclusively in the rectum, whereas NECs and MiNENs can occur within the whole colorectal tract with a slight preponderance in the right colon (Dasari et al. 2017; Klöppel 2015).

Macroscopically, rectal NETs usually present as small, well-circumscribed submucosal tumors that occur as polyps in the context of preventive endoscopic examination. Larger tumors show an infiltrative growth and tend to metastasize to regional lymph nodes and the liver. Histologically, rectal NETs show a well-differentiated neuroendocrine growth pattern and express cytokeratins, synaptophysin, and somatostatin receptor 2A (SSTR2A) as well as the pancreas-typical markers glucagon, pancreatic polypeptide, and ISLET1 (Klöppel 2013; Klöppel and Scherubl 2011; Konukiewitz et al. 2017). In contrast to PanNETs, the neuroendocrine marker chromogranin A is often negative in rectal NETs, while SATB2 is frequently expressed, which is of importance for differential diagnostic considerations concerning the site of origin in metastatic NETs (Klöppel and Scherubl 2011; Mohanty et al. 2021; Volante et al. 2021). Due to their very low proliferative activity, most rectal NETs are mostly graded as G1 or rarely G2 and small and localized NET are usually associated with an excellent prognosis (Dasari et al. 2017; WHO Classification of Tumours Editorial Board. Digestive system tumours 2019).

Systematic genetic studies on colorectal NETs are still scarce and so far, no pathognomonic genetic alterations have been identified.

NECs and MiNENs are macroscopically large, poorly circumscribed neoplasms, often with ulceration, hemorrhage, and necrosis. At the time of diagnosis, a large fraction of these tumors is locally advanced, show an involvement of regional lymph nodes and/or distant metastases (Jesinghaus et al. 2021; WHO Classification of Tumours Editorial Board. Digestive System tumours 2019). Histologically, colorectal NECs are poorly differentiated neoplasms with a diffuse, non-organoid growth pattern with necrosis and blunt mitotic activity that is mirrored by very high Ki-67 proliferation indices (WHO Classification of Tumours Editorial Board. Digestive System tumours 2019). The neoplastic cells are either "small, blue and round," show a high nucleus-to-cytoplasm ratio and a dense chromatin (NEC of small cell type, uncommon in colorectum), or possess large nuclei, with a vesicular chromatin and prominent eosinophilic nucleoli (NEC of large cell type). The (often dot-like) immunohistochemical expression of cytokeratins, synaptophysin, and INSM1 proves the epithelial and neuroendocrine nature of colorectal NECs.

MiNENs are by definition neoplasms with a neuroendocrine and a non-neuroendocrine component representing each at least 30% of the tumor mass. Almost all colorectal MiNENs represent mixed adenoneuroendocrine carcinomas (MANECs), that are composed of a morphologically variable adenocarcinoma component, that is usually combined with a large cell (or rarely) small cell NEC. The different components can be located separately from each other in separate clusters (mosaic type), closely intermingled in a cell-to-cell pattern (composite type), or even coexist within the same cell (amphicrine type) (Jesinghaus et al. 2017).

The frequent detection of alterations in *APC*, *KRAS*, *TP53*, *BRAF* and further mutations in genes linked to conventional carcinogenesis in colorectal NECs and MiNENs suggest a close relationship to conventional colorectal adenocarcinomas (Jesinghaus et al. 2017; Woischke et al. 2017). Separately analyzed neuroendocrine and non-neuroendocrine components of MiNENs exhibited a shared trunk of driver mutations (Jesinghaus et al. 2017).

NECs and MiNENs show a dismal clinical outcome that is considerably worse than the outcome of conventional colorectal adenocarcinoma including all of its morphologic variants (Jesinghaus et al. 2021; WHO Classification of Tumours Editorial Board 2019).

Clinical Presentation and Diagnosis

Matthias Schott

Colon

Clinical Symptoms and Signs

Colonic NECs usually present late, as large tumors, often with extensive metastatic disease when the diagnosis is made. The commonest symptoms are diarrhea, abdominal pain, gastrointestinal bleeding, or weight loss. Clinically, anemia, hepatomegaly, or a palpable abdominal mass may be present. Bowel obstruction, bleeding, and pain are possible presentations, similar to adenocarcinoma. Usually, the presumptive diagnosis of colonic adenocarcinoma is made until histology distinguishes the neuroendocrine nature. A tissue diagnosis is often made on colonoscopic biopsy. A frequent presentation is the presence of liver metastases at routine ultrasound of the liver. Overall, the most frequent presentation of all the cases is incidental finding at a routine endoscopy performed for other reasons and the second most common is rectal bleeding. Forty-five percent of colonic tumors are localized at diagnosis according to the SEER dataset, although in the smaller Spanish registry only 22.5% were localized.

Rectum

Clinical Symptoms and Signs

The majority of rectal NETs are localized at diagnosis (75–85%). They are usually incidental findings at sigmoidoscopy or colonoscopy (approx. 40%), with changes in bowel habit, rectal bleeding, anorectal symptoms (e.g., tenesmus, discomfort, or pain), and weight loss being rare. Malignant metastatic disease may present with right upper quadrant abdominal pain and hepatomegaly, lethargy, wasting, anorexia, or generalized symptoms of carcinomatosis. Bowel obstruction from rectal tumors is rare, but may occur with rectosigmoid or sigmoid lesions, or advanced intra-abdominal disease.

Diagnostic Imaging

Clarisse Dromain & Nicolas Villard

Colonic NECs are more frequently localized in the caecum and the ascending colon. On CT images, they have the same appearance as colorectal adenocarcinoma, presenting as a circumferential thickening or a polypoidal masses (Ganeshan et al. 2013). In metastatic tumor, the association with hypervascular liver lesions may be suggestive of the neuroendocrine type of the tumor.

In rectal NETs, MRI is recommended, in addition to CT, for patients with tumors > 10 mm (> T1) in size and/or node-positive tumors, in tumors not completely removed at endoscopy or if metastatic disease is suspected (Caplin et al. 2012). Rectal NEN is seen on MRI as a single submucosal mass with a homogeneous and marked contrast enhancement after contrast injection.

Surgical Treatment

Levant Dizdar & Wolfram Trudo Knoefel

Colonic NENs

The choice of treatment modality is based on the size, local spread, grading, and systemic dissemination of the colonic NETs. According to the 2012 ENETS guidelines, lesions < 2 cm may be removed endoscopically by polypectomy or endoscopic mucosal resection. In cases of incomplete resection, invasion of the muscularis propria or G2/G3 histology, oncologic colon resection with lymph node dissection should be performed according to the location of the primary tumor (Caplin et al. 2012). However, more recent guidelines recommend oncologic colon resection for tumors larger than 1 cm because lymph node metastases are expected in approximately 15% of tumors 1–2 cm in size (Al Natour et al. 2012; DGVS et al. 2018; Ito et al. 2021). For colon NETs larger than 2 cm, oncologic resection with lymph node dissection is generally recommended (Caplin et al. 2012; Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Ito et al. 2021). If surgical treatment is indicated, mesocolic resection with lymph node dissection should be performed according to the same standards applied for adenocarcinoma of the colon.

While resection of localized G1 and G2 NETs is associated with improved prognosis, the prognostic benefit of surgical resection for colonic NECs remains controversial (Balasubramanyam et al. 2019; Fields et al. 2019; Shafqat et al. 2015; Smith et al. 2014). In particular, surgery is generally not recommended for distant metastatic colonic NECs, but may be considered in highly select cases. In addition, in cases with acute symptoms such as subileus or ileus, palliative tumor resection, bypass surgery, or creation of a stoma can improve quality of life and avert short-term death from ileus (Shafqat et al. 2015; Smith et al. 2014).

Rectal NENs

The only curative treatment option for rectal NETs is complete tumor resection, which can be achieved either endoscopically or surgically, depending on the size, depth of infiltration, and grading of the neoplasia (Ramage et al. 2016). Lesions <1 cm and without involvement of the muscular wall can usually be completely removed with procedures such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or transanal endoscopic microsurgery (TEMS) (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Ramage et al. 2016). The optimal treatment of rectal NETs with a size between 1 and 2 cm is still unclear. The risk of metastasis of these lesions is estimated to be between 10% and 15% (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Shields et al. 2010). Several studies have shown that even rectal NETs between 1 and 2 cm in size can be resected safely and with excellent recurrence-free survival using endoscopic techniques (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; McDermott et al. 2014; Ramage et al. 2016; Shigeta et al. 2014; Yangong et al. 2014). Accordingly, most current guidelines recommend endoscopic resection even for 1–2 cm sized rectal NETs, if no infiltration of the muscular wall and G1 or G2 grading has been verified (Caplin et al. 2012; Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Ramage et al. 2016). Rectal NENs > 2 cm, or with infiltration of the muscular wall, with G3 grading, or locoregional lymph node involvement should be treated by anterior resection with total mesorectal excision or abdominoperineal extirpation corresponding to the distance to the anal verge (Caplin et al. 2012; Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Ramage et al. 2016).

Whether surgical resection of colorectal NECs confers a prognostic advantage remains controversial. Several studies have shown that surgical resection of colorectal highly proliferative NECs was not associated with improved prognosis in either localized or metastatic disease (Balasubramanyam et al. 2019; Smith et al. 2014). However, the largest study to date examining the association between different treatment modalities and survival in patients with colorectal NECs showed that both chemotherapy and surgery were associated with improved overall survival (Fields et al. 2019). Accordingly, the indication for resection of colorectal NECs should be discussed in interdisciplinary tumor boards and decided individually for each patient. Regardless of any survival benefit, surgical interventions to treat symptoms such as obstruction or bleeding may be warranted in patients with rectal NECs. A resection of the primary tumor may also be indicated for rectal NENs with unresectable distant metastases in order to control local tumor complications. (Caplin et al., Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018).

References

Al Natour, R.H., Saund, M.S., Sanchez, V.M. et al. (2012). Tumor size and depth predict rate of lymph node metastasis in colon carcinoids and can be used to select patients for endoscopic resection. *J Gastrointest Surg* 16 (3): 595–602.

Balasubramanyam, S., O'Donnell, B.P., Musher, B.L. et al. (2019). Evaluating treatment patterns for small cell carcinoma of the colon using the National Cancer Database (NCDB). *J Gastrointest Cancer* 50 (2): 244–253.

Caplin, M., Sundin, A., Nillson, O. et al. (2012). Barcelona consensus conference participants. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. *Neuroendocrinology* 95 (2): 88–97.

Dasari, A., Shen, C., Halperin, D. et al. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 3 (10): 1335–1342.

Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS), Netzwerk Neuroendokrine Tumoren (NeT) e.V. (Patientenvertretung), Bundesorganisation Selbsthilfe NeuroEndokrine Tumoren e.V. (NET-sgh) (Patientenvertretung), Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (DGHO), und Arbeitsgemeinschaft Internistische Onkologie (AIO) der Deutschen Krebsgesellschaft e.V, Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie e.V. (DGAV) et al. (2018). Practice guideline neuroendocrine tumors - AWMF-Reg. 021-27. *Z Gastroenterol* 56 (6): 583–681.

Fields, A.C., Lu, P., Vierra, B.M. et al. (2019). Survival in patients with high-grade colorectal neuroendocrine carcinomas: the role of surgery and chemotherapy. *Ann Surg Oncol* 26 (4): 1127–1133.

Ganeshan, D., Bhosale, P., Yang, T., and Kundra, V. (2013). Imaging features of carcinoid tumors of the gastrointestinal tract. *Am J Roentgenol* 201 (4): 773–786. doi:10.2214/AJR.12.9758. PMID: 24059366.

Ito, T., Masui, T., Komoto, I. et al. (2021). JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. *J Gastroenterol* 56 (11): 1033–1044.

Jesinghaus, M., Konukiewitz, B., Keller, G. et al. (2017). Colorectal mixed adenoneuroendocrine carcinomas and neuroendocrine carcinomas are genetically closely related to colorectal adenocarcinomas. *Mod Pathol* 30 (4): 610–619.

Jesinghaus, M., Schmitt, M., Lang, C. et al. (2021). Morphology matters: a critical reappraisal of the clinical relevance of morphologic criteria from the 2019 WHO classification in a large colorectal cancer cohort comprising 1004 cases. *Am J Surg Pathol* 45 (7): 969–978.

Klöppel, G. (2013). Neuroendokrine Neoplasien. In: M. Stolte, J. Rüschoff, and G. Klöppel (ed.), *Pathologie - Verdauungstrakt und Peritoneum*. Berlin Heidelberg.

Klöppel, G. (2015). Neoplasms of the disseminated neuroendocrine cell system of the gastrointestinal tract. *Pathologe* 36 (3): 237–245.

Klöppel, G. and Scherubl, H. (2011). Neuroendocrine neoplasms of the appendix and colorectum. *Pathologe* 32 (4): 314–320.

Konukiewitz, B., Schlitter, A.M., Jesinghaus, M. et al. (2017). Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20. *Mod Pathol* 30 (4): 587–598.

McDermott, F.D., Heeney, A., Courtney, D. et al. (2014). Rectal carcinoids: a systematic review. *Surg Endosc* 28 (7): 2020–2026.

Mohanty, S.K., Tiwari, A., Bhardwaj, N. et al. (2021). Positivity for SATB2 distinguishes Islet1 positive rectal neuroendocrine tumours from pancreaticoduodenal neuroendocrine tumours. *J Clin Pathol* 74 (9): 582–588.

Ramage, J.K., De Herder, W.W., Delle Fave, G. et al. (2016). ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. *Neuroendocrinology* 103 (2): 139–143.

Shafqat, H., Ali, S., Salhab, M., and Olszewski, A.J. (2015). Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. *Dis Colon Rectum* 58 (3): 294–303.

Shields, C.J., Tiret, E., and Winter, D.C., International Rectal Carcinoid Study G. (2010). Carcinoid tumors of the rectum: a multi-institutional international collaboration. *Ann Surg* 252 (5): 750–755.

Shigeta, K., Okabayashi, K., Hasegawa, H. et al. (2014). Long-term outcome of patients with locally resected high- and low-risk rectal carcinoid tumors. *J Gastrointest Surg* 18 (4): 768–773.

Smith, J.D., Reidy, D.L., Goodman, K.A. et al. (2014). A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol* 21 (9): 2956–2962.

Volante, M., Grillo, F., Massa, F. et al. (2021). Neuroendocrine neoplasms of the appendix, colon and rectum. *Pathologica* 113 (1): 19–27.

WHO Classification of Tumours Editorial Board. (2019). *Digestive System Tumours*, 5e. Lyon: International Agency for Research on Cancer (IARC).

Woischke, C., Schaaf, C.W., Yang, H.M. et al. (2017). In-depth mutational analyses of colorectal neuroendocrine carcinomas with adenoma or adenocarcinoma components. *Mod Pathol* 30 (1): 95–103.

Yangong, H., Shi, C., Shahbaz, M. et al. (2014). Diagnosis and treatment experience of rectal carcinoid (a report of 312 cases). *Int J Surg* 12 (5): 408–411.

Liver Metastases of Unknown Primary Neuroendocrine Neoplasms

Stefano La Rosa & Silvia Uccella

General Considerations

All neuroendocrine neoplasms (NENs) have metastatic potential, although the actual rate and pattern of metastatic dissemination depend on a variety of factors including the degree of morphological differentiation, proliferation grade (for neuroendocrine tumors, NETs), size, primary site of origin, and tumor cell type of each specific NEN (Uccella et al. 2021). Indeed, neuroendocrine carcinomas (NECs) have a higher intrinsic metastatic potential than NETs that, in turn, show a wide range of propensity to disseminate. Generally, the frequency of metastases in NETs is directly related to increasing primary tumor size and grade. However, the primary site has also a role in predicting metastatic dissemination: for example, it is well known that appendiceal and rectal NETs have a very low rate of metastases compared with primary NETs of other organs, such as the pancreas, the ileum, or the lung, which are, among NETs, the main source of liver metastases (Bellizzi 2013). Moreover, among NETs occurring in the same organ, different tumor cell types are related to different specific clinical manifestation and also to distinct tendency to give distant metastases. Just as an example, in the pancreas, insulinomas only rarely give rise to metastatic disease, whereas metastases from gastrinomas, glucagonomas, and ACTH-producing tumors, which are functioning neoplasms, are frequent (Maragliano et al. 2015). In a similar way, NETs of the same organ arising in the context of different clinicopathological conditions have different metastatic potential, as it is observed in the stomach. Here, NETs arising in the context of mucosal alterations associated with hypergastrinemia due to various causes (chronic atrophic gastritis, Zollinger-Ellison disease, or proton pump inhibitors abuse) are less prone to give metastases than gastric NETs arising in normal mucosa and in the context normal levels of circulating gastrin (La Rosa and Solcia 2020).

Overall, it has been reported that up to 90% of NECs and up to 40% of NETs, when symptomatic, present with synchronous metastases (Ramage et al. 2012; Riihimäki et al. 2016). The most frequent site for distant metastases of NENs is the liver, which is by far the favorite site for secondary localization of these neoplasms, followed by the peritoneum, the bone, and the lung (Riihimäki et al. 2016). About one-fifth of liver metastases from NENs are the initial clinical presentation of an occult neoplasm, the origin of which is unknown (Uccella et al. 2021). In such cases, the careful clinicopathological typing of the lesion represents the cornerstone for a correct patient's management. First, a distinction must be made between NEC and NET, as this is the single most important determinant of the therapeutic choice. In the case of NEC, the identification of the site of origin is not possible on morphological and immunohistochemical ground, but, however, this is of limited interest as independently of where the tumor comes from, the patient's treatment relies on platinum-based schedules, firstly optimized for pulmonary small cell and large cell NECs (Mollazadegan et al. 2021). In contrast, the recognition of a metastatic NET requires the recruiting of every effort, from both the clinician's and the pathologist's side, to identify the site of origin of the neoplasm, as the therapeutic approach may vary depending on the primary site and cell type. For example, even when liver metastases are unresectable, there is some evidence that the surgical treatment of a primary ileal NET has a positive impact of patient's outcome (Frilling et al. 2014).

Pathology

In the diagnostic management of a metastatic NEN to the liver, pathologists are often faced with small core needle biopsies, with frequent crush artifacts. Consequently, morphology alone may not be enough for even establishing the diagnosis of NEN and the proper application and interpretation of selected immunohistochemical markers are of help. First, NENs are to be distinguished from non-neuroendocrine neoplasms, and this can be achieved by the application of general neuroendocrine markers, of which synaptophysin, chromogranin A, and INSM1 are the most sensitive and specific ones (Uccella et al. 2018). The expression of one, or better two, general neuroendocrine markers is required for establishing a diagnosis (Rindi et al. 2022). It should be also recalled that non-epithelial NENs (pheochromocytoma/paraganglioma) do exist and may be metastatic, thus, the application of a pan-cytokeratin stain is not redundant in a proper immunohistochemical panel (Uccella et al. 2018). Once the diagnosis of epithelial NEN is established, the distinction between NET and NEC is, as already mentioned, of paramount importance. In presence of a questionable/altered morphology, a panel of immunostains for Ki67, p53, Rb, somatostatin receptor 2A (SSTR2A), chromogranin A and, in the suspect of a pancreatic primary, DAXX/ATRX may be useful to solve this issue (Uccella et al. 2018) (Figure 10). In the case of NET, a complete typing of the neoplasm, including proliferation grade and tumor cell type identification, is crucial for therapeutic decision-making, often avoiding unnecessary further biopsies on the primary site (Frilling et al. 2014).

When the liver metastasis is the only clinically observable presentation of the disease, the diagnosis of a NET engages the pathologist, as well as the oncologist, in the search for the site of origin of the neoplasm. Indeed, immunohistochemistry offers a spectrum of useful tools, ranging from transcription factors to hormones, to other site-specific markers that can be helpful for this purpose (Table 8) (Asa et al. 2021; Duan and Mete 2016; Uccella et al. 2018). Nevertheless, it is worth noting that the sensitivity and specificity of different markers is not high enough to allow the use of a single immunostaining for the diagnosis. Thus, a reasoned panel including positive and negative markers is recommended. In diagnostic practice, an algorithmic approach implying the sequential application of selected markers seems the best way to avoid waste of time and of financial resources (Bellizzi 2020; Luchini et al. 2021).

In summary, after the initial confirmation of the epithelial and neuroendocrine nature of the proliferation using pan-cytokeratins and general neuroendocrine markers (synaptophysin,

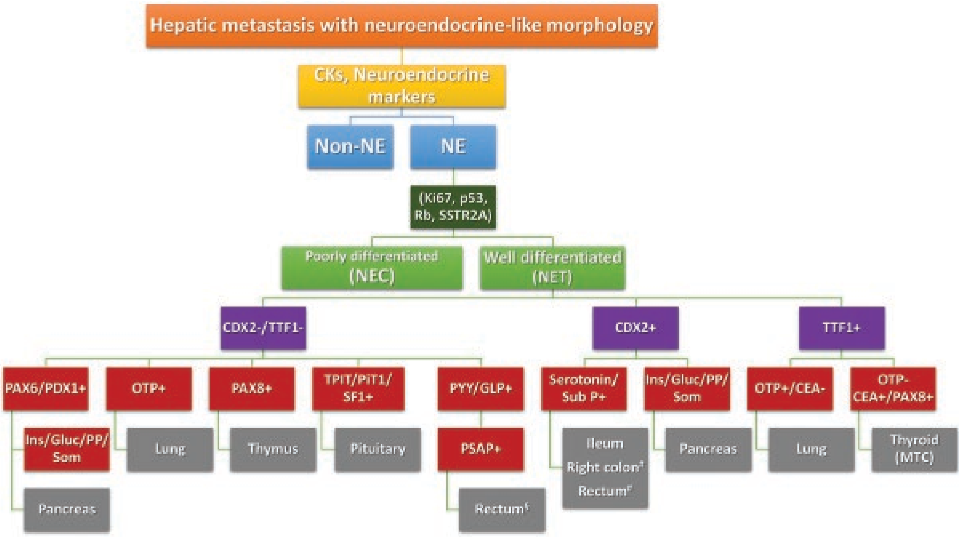

Figure 10 Practical algorithm for the immunohistochemical management of liver metastases from neuroendocrine neoplasms of unknown primary site. §, L-cell NET; #, EC-cell NET (modified from Luchini et al. 2021).

Table 8 Useful immunohistochemical markers for the identification of the occult primary site of a neuroendocrine tumor (modified from Luchini et al. 2021).

Putative primary site	Transcription factors	Hormones	Other markers
Pituitary	Pit1, SF1, Tpit, ER-α, GATA-2, GATA-3	PRL, GH, TSH, ACTH, FSH, LH, α-SU	
Thyroid	PAX8, TTF1	Calcitonin	CEA, CGRP
Parathyroid	GATA-3	PTH	
Lung	TTF1, OTP	Bombesin, serotonin, calcitonin	
Stomach	CDX2	(Histamine), serotonin, ghrelin	VMAT2
Duodenum	ISL1, PDX1, CDX2	Somatostatin, gastrin, serotonin	
Pancreas	ISL1, PAX6, PDX1, CDX2, Nkx6.1, PgR	Insulin, glucagon, PP, somatostatin, gastrin, VIP, ACTH, serotonin, calcitonin, others	
Jejunum/Ileum	CDX2	Serotonin, substance P	VMAT1
Appendix	CDX2	Serotonin, glucagon-like peptides	VMAT1
Colon-rectum	SATB2 (L-cell NET) CDX2 (EC-cell NET)	PYY, PP, glucagon-like peptides, serotonin	Prostatic acid phosphatase
Paraganglioma	GATA-3	(Cathecolamines)	Tyrosine hydroxylase, VMAT1, VMAT2

chromogranin A, and INSM1), the differential diagnosis between NEC and NET and the grading of the latter may require the use of Ki67 and other markers (p53, Rb, SSTR2A). The search for an unknown primary may start with the use of CDX2 and TTF1 that helps in identifying the most frequent site of occurrence of metastatic neoplasms to the liver (ileum, pancreas, and lung). An immunoreactivity for CDX2 points toward a midgut (small intestinal) or pancreatic origin (Figure 11), whereas TTF1 is reminiscent of a lung primary (Figure 12). The additional use of the transcription factors PDX1 and PAX6, which has been reported to have a certain specificity for pancreatic NETs, may be considered, although, even in expert hands, the immunoreaction with commercially available antibodies may be difficult to evaluate. In CDX2-positive metastases, the employment of antibodies directed against hormonal products like serotonin or pancreatic hormones may give clues to an ileal or pancreatic origin, respectively. However, it should be recalled that EC-cell NETs similar to those arising in the ileum may be also observed in the large intestine, including rectum, and in other rare sites, such as the pancreas and the ovary. TTF1-positive NETs are frequently of pulmonary origin, albeit TTF1 is not entirely specific for these neoplasms as, in the context of NENs, also medullary thyroid carcinoma (MTC) is TTF1-positive and, in turn, calcitonin expression is not an absolutely specific marker of MTCs, as also lung NETs may stain positively for this hormone. In such case, a positive stain for PAX8 and CEA favors MTC versus lung NET (Figure 13). OTP (orthopedia homeobox protein) has been reported as a very specific marker for lung NETs showing higher sensitivity than TTF1. Other additional markers may be of help in confirming, for example, an ileal (Substance P), colo-rectal (prostatic acid phosphatase, PSAP), gastric (vesicular monoamine transporter 2, VMAT2), or duodenal (gastrin, somatostatin) primary. Liver metastases from NETs arising in rare sites (extra-GEP and extra-thoracic) are possible findings and also in this case immunohistochemistry may be of help (Table 8). For example, the possibility of metastases from pituitary NETs should not be underestimated, particularly in the clinical context of Cushing syndrome (Venable et al. 2020). In this case, the use of pituitary-specific transcription factors is useful to reach a correct diagnosis. Finally, it should be considered that, even if the immunohistochemical armory may not be resolutive in finding an unknown primary site of the metastatic NETs, the positive immunostaining for somatostatin receptors is predictive of the avidity of the neoplasm for somatostatin analogues-based imaging that can lead to the identification of the primary NET (Volante et al. 2007).

As above discussed, the use of specific immunohistochemical panels, including different transcription factors and hormones, associated with morphological features allows the identification of the primary site of an occult metastatic NET in most of cases. However, it is worth noting that this approach is not valid in presence of an occult metastatic NEC, the morphology of which is always the same independently of the site of origin. In addition, transcription factor expression in NECs does not respect the origin. Indeed, NECs arising in extra-pulmonary sites may express TTF1 and, conversely, CDX2 expression has been reported in lung large cell NECs (Uccella et al. 2018). For this reason, pathologists cannot suggest a possible origin of an occult metastatic NEC, which can be identified using an imaging approach.

Diagnostic Imaging

Clarisse Dromain & Nicolas Villard

Liver MRI has become a cornerstone in the evaluation of NEN patients from diagnosis to follow-up. MRI is more sensitive (95.2%) when compared to other modalities like computed

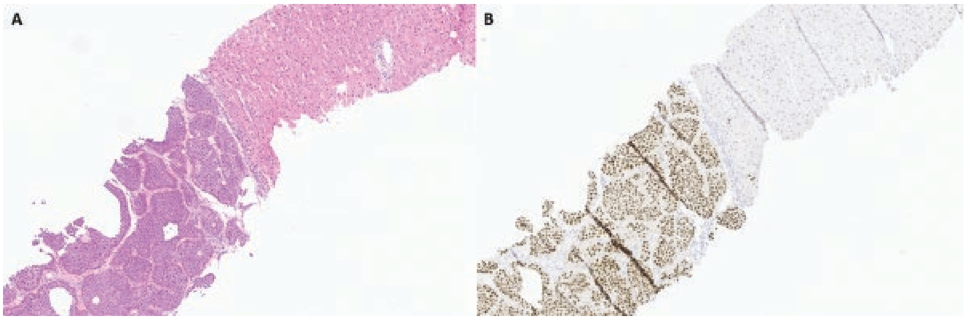

Figure 11 Liver metastasis from an occult NET showing a nested architecture and composed of cells with abundant eosinophilic cytoplasm (A). Tumor cells show nuclear immunoreactivity for CDX2 (B). The morphological features and the CDX2 expression suggested the midgut as the site of the primary tumor. The primary tumor was identified in the ileum.

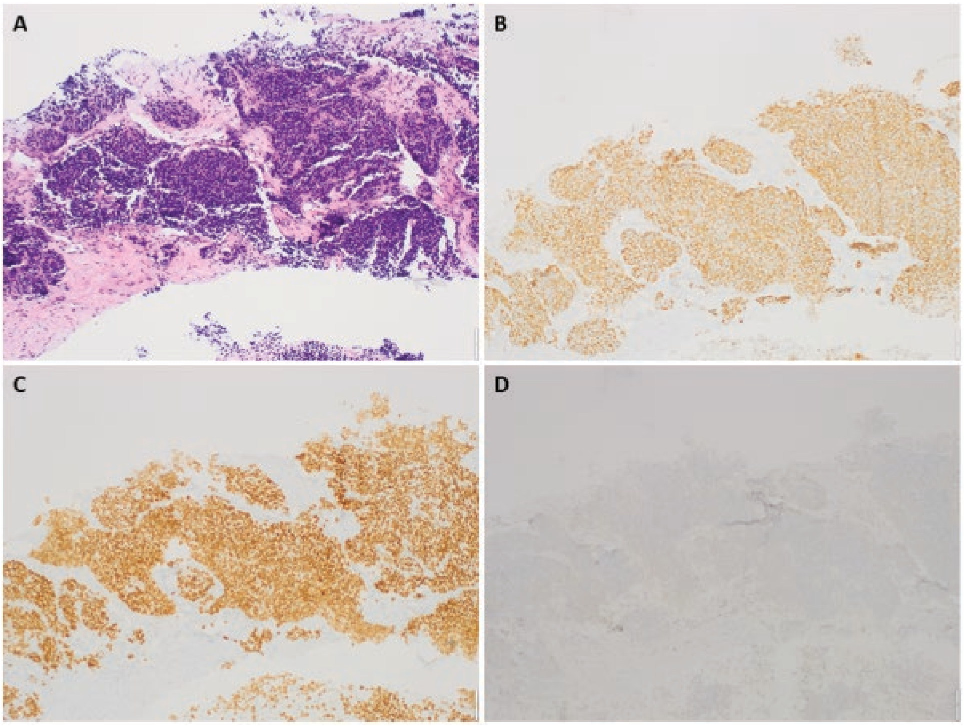

Figure 12 Liver biopsy showing a metastatic tumor with crush artifacts rendering difficult the morphological interpretation. Tumor shows an organoid architecture (A) and chromogranin A (B) expression suggesting the neuroendocrine nature of the lesion. The strong immunoreactivity for TTF1 (C) and the lack of CDX2 (D) expression suggested the lung origin of the primary, where it was then actually found.

tomography (CT) (78.5%) and somatostatin receptor scintigraphy (49.3%) for the diagnostic of NEN liver metastases (NELM) (Dromain et al. 2005). Due to their particular arterial supply, NELMs are known to present a hypervascular pattern in the arterial phase in a majority of the patients (70–73%) (Dromain et al. 2003; Ronot et al. 2017). However, about 30% of NELMs show various patterns, including a hypoenhancing pattern on both arterial and portal phase in 12%, which explains the variable lesion conspicuity seen with dynamic phase. Diffusion-weighted imaging and more recently, the hepatobiliary phase after injection of liver-specific MR contrast agent (mainly gadoxetic acid, Primovist, Bayer Schering Pharma) has been shown to be the most sensitive for the detection of NET liver metastases (d'Assignies et al. 2013; Hayoz et al. 2020). Due to the lack of normal hepatocytes, NELMs as all other liver metastases, appear hypointense (eventually with target appearance) compared to the liver parenchyma during the hepatobiliary phase.

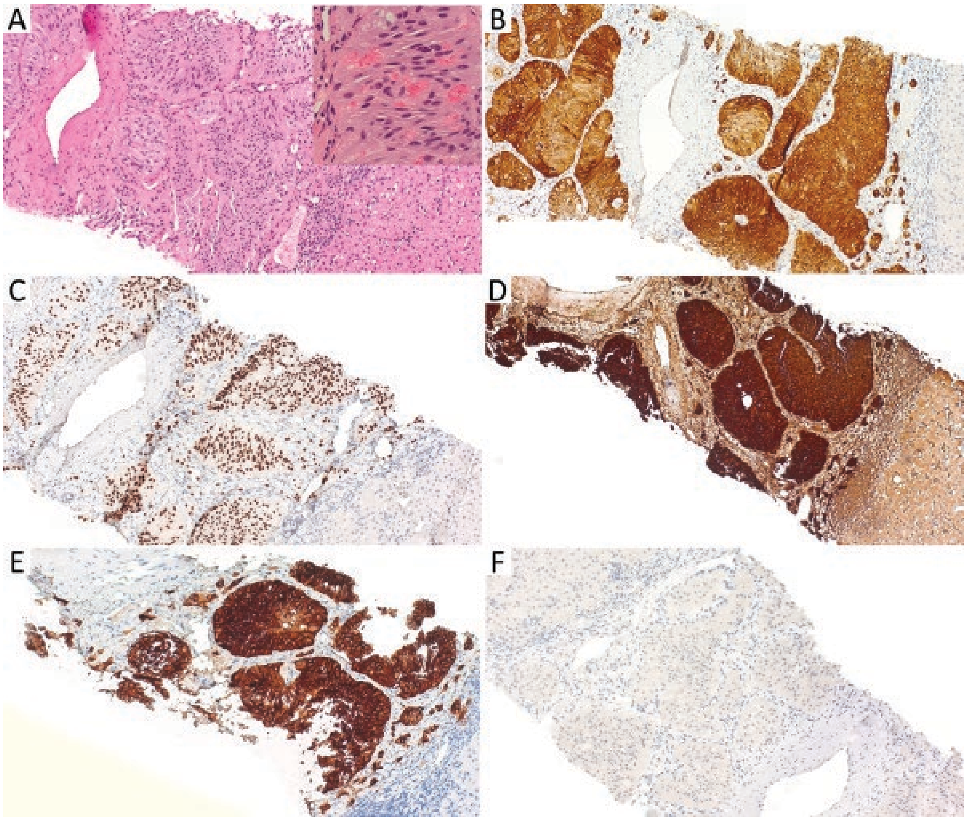

Figure 13 Liver biopsy showing a metastasis composed of spindle cell with eosinophilic cytoplasm (A). Tumor cells are strongly positive for chromogranin A (B), TTF1 (C), calcitonin (D), and CEA (E). CDX2 expression is lacking (F). This immunophenotype is in line with the diagnosis of medullary thyroid carcinoma, that was identified in the thyroid (Courtesy of dr. Amedeo Sciarra and dr. Charles Bénière, Histopathology, Central Institute, Valais Hospital, Sion, Switzerland).

Imaging also plays a major role in the prognostic characterization of the liver metastases from NENs. Parameters of importance are:

- Tumor burden: the percentage of liver involvement and the number of metastatic sites are prognostic parameters (Palazzo et al. 2013).
- Liver metastases vascularization: vascularization shown in contrast enhanced images is a parameter of importance in selecting appropriate treatment, in particular in the selection of patient that could be good candidate for transarterial chemoembolization (TACE). Enhancing tumor burden has been shown to be the major parameter to predict efficacy of TACE and also the more accurate parameter for early assessment of TACE with the volumetric change of the enhancing tumor volume being correlated with response and overall survival (Sahu et al. 2017).
- The spontaneous tumor progression slope. In the study of Durante et al., an independent statistical correlation was found between tumor slope before treatment and survival of metastatic GEP tumors (Durante et al. 2009). This parameter was found to better reflect tumor aggressiveness than disease-free interval or proliferative index. Most authors consider a low slope if RECIST sum <20% over 1 year. Another way to assess the spontaneous tumor growth is to measure the TGR (tumor growth rate), defined as an estimate of the increase/decrease of the tumor volume over time. TGR is expressed as the percentage change in tumor volume over 1 month. In post-hoc analyses, tumor measurements from CLARINET were reevaluated to explore the clinical utility of TGR (Dromain et al. 2019). A pretreatment TGR >4%/month was associated with a 4.1-fold greater risk of progression than TGR ≤ 4%/month in the overall population (HR 4.1 [95% CI 2.5, 6.5]; p<0.001, n=187). This study also suggests a higher prognostic role of TGR than the histologic grade. The TGR at 3 months from the start of treatment was also identified as an early biomarker able to predict PFS at 1 year in grade 1 and 2 GEP-NENs.

Local Therapy: The Role of Interventional Radiology in the Treatment of NELM

Clarisse Dromain & Nicolas Villard

Local nonsurgical liver-targeted therapies can be considered in the context of NENs with progressive, unresectable NELM and/or hormonal syndromes refractory to conventional medical treatment or in the purpose of downstaging a bulky disease (Machairas et al. 2021).

Thermal ablation (TA) including radiofrequency (RFA) and microwave ablation (MWA) of focal tumors is based on high-temperature tissue heating (>50°C) targeted by applicators placed percutaneously in or around a tumor to induce coagulation necrosis. Based on the solid data on colorectal liver metastasis, TA appears to be an effective alternative to surgery for patients with limited NELM liver disease (up to five liver metastases, each measuring <3 cm in diameter). Tolerance is excellent and complications (e.g., bleeding, nontarget thermal damage) are very rare. A recent retrospective study showed no difference of overall survival between patients treated by surgery and MWA. Length of stay and complication rates (5%) were significantly lower for patient treated by MWA with an excellent local control (98.2%) (Perrodin et al. 2020).

In contrast to patients selected for RFA/MWA, transarterial embolization (TAE) and chemoembolization (TACE) is mostly indicated for patients with multiple non-resectable NELM and a more advanced liver tumor burden. NELM mostly depends on the arterial system vascularization whereas normal adjacent liver is mostly supplied by the portal system. Around 70% of NELMs are hyper-enhancing during the arterial phase (Dromain et al. 2003). The remaining of NELMs have a necrotic component and are less sensitive to arterial occlusion. Bland trans-arterial embolization (TAE) consists of injection of particles such as gelatin sponge, polyvinyl alcohol, or calibrated microspheres to occlude targeted territories. Conventional TACE (c-TACE) is the infusion of chemotherapeutic agents (e.g., doxurubicine or idarubicine) emulsified with ethiodized oil (lipiodol), with or without additional embolization by particles. Drug-eluting beads TACE (DEB-TACE) is the administration of calibrated microspheres onto which chemotherapeutic medication is loaded or adsorbed with the intention of sustained in vivo drug release. A tumor burden greater than 50–90% is a relative contraindication that can be balanced by sequential treatment (Barat et al. 2020). No available evidence exists that one trans-arterial technique is more effective than the others are but TAE may be rather safer than TACE. The ongoing randomized embolization trial for NELMs (RETNET) aims at comparing bland embolization, Lipiodol® chemoembolization, or DEB chemoembolization, with 60 patients per arm (Chen et al. 2018). Recently, the first safety review reported serious adverse effects in the DEB arm that was then closed supporting previously reported high risk of biliary complications, liver infarct, and necrosis for liver metastasis treated with DEB-TACE (Chen et al. 2018). Therefore, bilio-enteric anastomosis should be considered as a contraindication for TAE/TACE. Tolerance of TAE/TACE can be improved by splitting the treatment. However, the pain during the arterial occlusion is almost always followed by a post-embolization syndrome that could last up to 2 weeks (Barat et al. 2020). Although the risk of developing liver abscess after TAE/TACE is five times higher for NELM than for other primary tumors, mortality after TAE/TACE remains low (0–8%) with most deaths related to toxic carcinoid syndrome or liver failure (Barat et al. 2020). Therapeutic response was only evaluated by large retrospective studies that reported decrease of liver mass effect in all patients, improvement of symptoms in 60–90% of patients. Objective response (RECIST, mRECIST) was reported in 50–90% of cases but no complete response was achieved. Biological anomalies were normalized in approximately half the cases (Barat et al. 2020).

Like TAE and TACE, selective internal radiation therapy (SIRT) is generally indicated in patients with NELM not amenable to hepatic resection. Most SIRT use resin or glass microspheres, with diameter larger than the hepatic capillaries, loaded with yttrium 90 (90Y), a pure beta-emitter with a physical half-life of 96 h and a radiation penetration of 2.5–10 mm. Treatments are planned during multidisciplinary meetings with nuclear medicine physician, physicists, and interventional radiologists. SIRT is often called “radio-embolization” (RE) but this term should be avoided as the embolic effect of the treatment is not the major goal. The treatment is divided into two phases. During the first phase, targeted territories will be selectively microcatheterized. Coiling can be performed in order to avoid nontarget irradiation with a careful attention on digestive tract perfusion. As for conventional trans-arterial therapies, conebeam-CT or 4D-CT are highly recommended. Then, a dose of technetium-99-labeled macro-aggregate albumin (99mTc-MAA) is injected and the precise position of the microcatheter is recorded. Immediately after, SPECT is realized to evaluate tumor-delivered dose, normal liver-delivered dose, extra-hepatic perfusion, and especially the hepatopulmonary shunt. SIRT is contraindicated if hepatopulmonary shunt (HPS) is greater than 20%. Based on volumetric and dosimetric data, a personalized dose of 90Y is then calculated. During the second phase, the microcatheter is placed at the exact same position than for the MAA injection and the 90Y spheres are then infused. Available literature about SIRT for NELM is heterogeneous with symptom control, tumor response rates, and survival outcomes varying significantly. Two recent large meta-analyses reported median overall survival up to 32 months and symptoms were improved in 20–80% of patients. Objective response rates (RECIST, mRECIST) were recorded among up to 18% of the patients. Unlike TACE/TAE, some complete responses after SIRT were observed (Frilling et al. 2019; Jia and Wang 2018). Despite concentration of deposition of radioactive microspheres in the hyper-vascular tumors, non-tumoral liver parenchyma is also irradiated and liver toxicity is constant but remains mostly asymptomatic and tolerance is excellent. Radioembolization induced liver disease (REILD) is a dreadful potentially life-threatening complication occurring in 0–13% of cases. Increased baseline level of bilirubin is a well-known risk factor for REILD (King et al. 2008).

Surgical Treatment of NELM

Levant Dizdar & Wolfram Trudo Knoefel

Even in metastatic disease, surgery plays an important role given the rather indolent behavior of a large fraction of GEP-NENs (Frilling et al. 2014; Pavel et al. 2020). Meticulous patient selection is essential for improving the perioperative and long-term outcomes related to hepatic resection for NELM. Whether resection of NELM is reasonable depends on several parameters. In general, no or only minimal extrahepatic disease should be present, the primary tumor should be completely resectable, and the patient should not exhibit any comorbidities that limit life expectancy or significantly increase the risk of surgery. In addition to these general requirements for surgery of hepatic metastases, the indication for resection of NELM is particularly influenced by tumor differentiation and grading. Resection of hepatic metastases is commonly indicated for tumors with well-differentiated morphology and low to intermediate grading (G1/G2). A recommendation for or against resection of liver metastases from the recently defined subgroup of well-differentiated but highly proliferative NETs G3 can hardly be given due to a lack of sufficient data. Accordingly, current guidelines do not clearly recommend resection, but state that surgery should not be excluded for patients with NETs G3 liver metastases (Pavel et al. 2020). In contrast, hepatic metastases from poorly differentiated NECs are considered an absolute contraindication to surgery in previously published guidelines (Garcia-Carbonero et al. 2016; Pavel et al. 2016, 2020). However, limited evidence indicates that liver resection may also be beneficial in well-selected patients with NECs, particularly those with a Ki-67 index <55% (Galleberg et al. 2017). Correspondingly, surgical resection may be considered in individual cases of metastatic NECs. However, the potential benefit of surgical treatment must always be weighed against the risk of postoperative complications and rapid disease progression after surgery. Another crucial factor for considering a surgical approach is whether complete resection of the metastases is possible or not. The 5-year overall survival (OS) rate after curative resection (R0, R1) of GEP-NETs with hepatic metastases is approximately 85%. Accordingly, surgical resection should be pursued for potentially resectable disease (Frilling et al. 2009; Pavel et al. 2020). The main factor determining the feasibility of resection is the future liver remnant (FLR) after resection. The latter should comprise approximately 25% of the standardized liver volume and have an intact venous, arterial, portal venous and biliary vasculature (Vauthey et al. 2000). In critical cases, the volume and function of the FLR should be estimated using techniques such as CT volumetry and hepatobiliary scintigraphy (de Graaf et al. 2010; Vauthey et al. 2000). In patients with insufficient FLR, portal venous embolization (PVE) or in-situ split plus portal vein ligation may be useful to augment the FLR. In addition, for patients with bilateral NET-LM, a combination of resection and ablative procedures such as RFA may be used. Resection is performed for the dominant lesion, whereas ablation is used to treat small lesions in the FLR.

Liver Transplantation

For highly selected GEP-NET patients with unresectable liver metastases, liver transplantation may be a reasonable treatment option. In 2007, Mazzaferro et al. developed the Milan criteria for NET-LMs. According to these criteria, patients with a confirmed Ki-67 proliferation index < 10%, a primary tumor that is drained by the portal system, a liver involvement of < 50%, complete resection of the primary tumor and all extrahepatic disease, with good response or stable disease for at least 6 months before transplant consideration and age <60 years are suitable candidates for liver transplantation (Mazzaferro et al. 2007). In these selected patients remarkable 5- and 10-year survival rates of 97% and 89%, respectively, were achieved (Mazzaferro et al. 2016).

Surgical Treatment of Metastatic NENs of Unknown Primary (NEN-CUP)

In the case of an abdominal manifestation of well-differentiated (G1/G2) NETs of unknown origin (NET-CUPs) diagnostic laparotomy should be considered in operable patients. Surgical exploration can be used both diagnostically to search for a primary tumor as well as with a curative intent in the cases of non-diffuse metastasis (Begum et al. 2014; DGVS et al. 2018). As small intestinal NENs are the most common cause of NEN-CUP syndrome, the entire small intestine should be screened bimanually. Rarely, pancreatic or duodenal NENs may be the cause of CUP syndrome, thus exploration of these sites and intraoperative sonography of the pancreas should be considered. In many cases, the primary tumor can be localized, but even without evidence of a primary tumor, resection of metastases can show good long-term success (Begum et al. 2015; Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018).

Medical Therapy and Chemotherapy of GEP NENs

Christoph Roderburg & Henning Jann

Introduction

Neuroendocrine neoplasms are very heterogeneous tumors and encompass a wide range of therapeutic options (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018). The number of available phase III studies is limited, and comparative studies are lacking for most situations. Therefore, especially in the metastatic situation, a determination of the therapeutic procedure after discussion in an interdisciplinary tumor conference is recommended (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018). In patients with advanced well-differentiated neuroendocrine tumors, systemic therapy is given to control the tumor associated clinical symptoms on the one hand and to control the tumor growth on the other (Pavel et al. 2020). Thus, accurate determination of the therapeutic target is crucial for therapy selection, in addition to knowledge of the tumor localization and extent, pathological and clinical features, growth behavior and SSTR imaging. Based on these criteria and considering the current guidelines for the management of neuroendocrine neoplasms, we comprehensively discuss the available knowledge on drug therapy of NEN.

Treatment for Symptom Control

Somatostatin analogues are able to inhibit the release of bioactive peptides and amines and thus alleviate symptoms of carcinoid syndrome (Stueven et al. 2019). In approximately two-thirds of patients, adequate symptom control can be achieved with the administration of somatostatin analogues. The rate of side effects from this treatment is low, therefore, SSAs are considered as gold standard in the first-line therapy of carcinoid syndrome (Stueven et al. 2019). Octreotide and Lanreotide are the best analyzed drugs in this setting. In cases of inadequately controlled carcinoid syndrome, various additional modalities are available, but these have not been compared with each other (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018). Pasireotide LAR may be considered in subsets of patients when established options failed (Wolin et al. 2015). In addition, interferon alpha (IFN-a) has demonstrated similar efficacy in achieving symptom control when compared with Octreotide or Lanreotide but with significantly higher side effects (Oberg 2000). Therefore, it is mostly used in patients with symptoms refractory to SSA. In addition, the orally available serotonin synthesis inhibitor Telotristat ethyl may provide relief of diarrhea in the setting of carcinoid syndrome. In a randomized phase III trial (TELESTAR), 135 patients with metastatic NENs and non-adequately controlled carcinoid syndrome were treated at a dose of 250 mg or 500 mg Telotristat ethyl 3 times daily while maintaining somatostatin analogue therapy (Kulke et al. 2017a). Compared to placebo, there was a significant decrease in stool frequency in both dose groups. A second placebo-controlled trial (TELECAST) supported the efficacy and good tolerability of telotristat ethyl (Pavel et al. 2018). Other treatment options for uncontrolled symptoms include surgery, local ablative measures, PRRT, and Everolimus (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018). Notably, the sequence in which to proceed with inadequately controlled carcinoid syndrome, in the absence of comparative studies, can only be based on the individual case and should include aspects such as comorbidity, treatment risks, treatment feasibility, and patient preferences, preferably with the involvement of an interdisciplinary tumor board (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018, Pavel et al. 2020).

Antiproliferative Medical Treatment Options

Antiproliferative medical treatment options include targeted drugs and systemic chemotherapy. All available drugs do not provide cure but may prolong patients' survival and quality of life.

Somatostatin Analogues

In addition to numerous phase II studies with predominantly mixed patient populations, the value of somatostatin analogues in antiproliferative intention has been confirmed by data of two prospective randomized placebo-controlled phase III studies, namely the PROMID- and the CLARINET-trial (Caplin et al. 2014; Rinke et al. 2009). The PROMID-trial revealed a prolongation of time to tumor progression by 8.3 months in patients receiving octreotide LAR 30 mg compared to placebo (14.3 vs. 6 months; HR 0.34; $p < 0.001$). The most favorable results were found in patients with low hepatic tumor burden (<10%). Patients with both functionally inactive tumors and with mild carcinoid syndrome were included. The majority of study patients had scintigraphically receptor-positive tumor, but this was not an inclusion criterion (Rinke et al. 2009). In the CLARINET study, patients with metastatic, functionally inactive, somatostatin receptor-positive enteropancreatic NETs or NETs with unclear primary with a proliferation index of Ki-67 <10% were treated with lanreotide autogel 120 mg every 4 weeks or placebo. Lanreotide was associated with a significant increase in progression-free survival (median not reached versus 18 months; HR 0.47; $p < 0.001$). The benefit was more pronounced in patients with midgut NETs (HR 0.35; $p = 0.009$) than in the pancreatic subgroup (HR 0.58; $p = 0.06$); (Caplin et al. 2014). In summary, according to the current ESMO guidelines, SSAs can be recommended for *"tumour growth control in advanced SSTR-positive, slowly-growing GI and Pan-NETs up to a Ki-67 of 10%."* This recommendation is valid for patients with unknown disease status, stable or progressive disease. According to these guidelines, *"(…) positive SSTR status is generally required but is not predictive of response"* (Pavel et al. 2020).

Everolimus

Everolimus has proven activity in pancreatic-, gastrointestinal, and pulmonary NETs. In progressive pancreatic NETs, Everolimus has been studied in several trials (RADIANT-1, RADIANT-3, COOPERATE-2); (Kulke et al. 2017b; Yao et al. 2010, 2011). Progression-free survival ranged from 9.7 to 16.6 months; response rates were < 10% in all trials. The registration trial (RADIANT-3 study) showed prolongation of PFS by 6.4 months in advanced progressive pancreatic NETs, median PFS was 11 months with everolimus and 4.6 months with placebo (Yao et al. 2011). There was a trend toward OS benefit (Yao et al. 2016b). Based on the negative results from COOPERATE-2, combination therapy of SSA and everolimus is not recommended. In extrapancreatic NET, everolimus was tested within the RADIANT-2 and RADIANT-4 trial (Pavel et al. 2011; Yao et al. 2016a). The RADIANT-2 trial included patients with progressive NET and carcinoid syndrome (primary in the small bowel in 51 and 53% in the two treatment arms, respectively). Patients were treated with everolimus plus octreotide or placebo plus octreotide, respectively. Median PFS was prolonged by 5.1 months in the everolimus group; however, the difference did not reach statistical significance. Subgroup analyses showed efficacy of the treatment regimen in NETs of the small bowel and NETs of the colorectum. Of note, the final OS results from the RADIANT-2 trial indicate a trend toward unfavorable OS in the everolimus arm. Therefore, *"everolimus should be used with caution if considered for patients with carcinoid syndrome"* according to the current ESMO guideline (Pavel et al. 2020). The RADIANT-4 trial included patients with nonfunctional NETs G1/G2 of the lung and GI tract (Yao et al. 2016a). The median PFS of the overall cohort was 11.0 months in the everolimus arm versus 3.9 months in the placebo arm ($p < 0.001$). In a post-hoc subgroup analysis, efficacy was shown for all GI-NETs as well as for lung-NETs. Typical side effects of everolimus include stomatitis, hyperglycemia, diarrhea, infections, and rarely pneumonitis. Across all trials, around 60% required dose reduction or treatment interruption.

Sunitinib

Sunitinib was evaluated in a placebo-controlled trial in progressive pancreatic NETs. It showed a prolongation of progression-free survival from 5.5 months with placebo to 11.4 months with sunitinib (Raymond et al. 2011). There was a trend toward an OS benefit with sunitinib, ORR was less than 10% (Raymond et al. 2011). About two-thirds of the patients had prior systemic therapy (usually chemotherapy), one-third even two systemic therapies. Most frequent side effects included diarrhea, nausea, asthenia, vomiting, and fatigue (32%). Results of a phase IV trial confirmed the efficacy and safety of sunitinib in patients with advanced, well-differentiated Pan-NETs who were treatment-naive or previously treated with other drugs (Raymond et al. 2018). Of note, there are no comparative studies of everolimus vs. sunitinib in pancreatic NETs. Only very few data exist for the use of sunitinib in patients with extrapancreatic NET and – outside of clinical trials – the use of sunitinib should be restricted to patients with pancreatic NETs. Other TKI currently tested in patients with NETs include surufatinib, lenvatinib, and cabozantinib, potentially expanding treatment options for patients with neuroendocrine tumors in the future (Rindi and Wiedenmann 2020).

Interferon-α

Also due to the lack of other substances, the administration of interferon alpha represented a standard in the antiproliferative therapy of neuroendocrine tumors for a long time. This practice is supported by data from a randomized trial (including 35% midgut NETs) showing a, median PFS 15.4 months for IFN-α and octreotide LAR (Yao et al. 2017) and retrospective analyses (Oberg and Eriksson 1991). Since better tolerated substances have become available, interferon alpha should only be used if other treatment options have been exploited or are not feasible (e.g., SSTR-negative status), particularly in patients with midgut NETs (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Pavel et al. 2020).

Systemic Chemotherapy

Results with systemic chemotherapy for advanced well-differentiated NETs are dependent on the tumor origin. At present, there is no established chemotherapy for extrapancreatic NET (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Pavel et al. 2020). Experience is only available from heterogeneous, small studies and the objective tumor responses are generally low. Only in selected patients with higher probability of response (e.g., higher Ki-67 >15%; significant progression) chemotherapy might be considered (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Pavel et al. 2020). In contrast, systemic chemotherapy might be indicated in patients with non-resectable metastases from well-differentiated pancreatic NETs. In this setting streptozotocin-based chemotherapy regimens show high objective tumor response rates of about 40% and might be given upfront in bulky disease even without documented prior tumor progression (Dilz et al. 2015). Similarly, Temozolomide-based chemotherapy regimens show high objective response rates in pancreatic neuroendocrine tumors. Recently, retrospective analysis suggested that temozolomide is active either alone or combined with capecitabine (Cives et al. 2016). A recent prospective explorative phase II trial comparing the efficacy of capecitabine plus temozolomide with that of temozolomide alone in patients with progressive pancreatic neuroendocrine tumors suggested superiority of the combination therapy with respect to PFS prolongation (22.7 months versus 14.4 months, respectively). Despite being preliminary, these data argue for the combination at least in patients suitable for intensive treatments. Oxaliplatin-based chemotherapy with FOLFOX or XELOX may be considered for the therapy of GI NET after exhaustion of established therapeutic options as fourth-line therapy on a case-by-case basis. Oxaliplatin-based chemotherapy with FOLFOX or XELOX demonstrated an ORR of 26% and stable disease in 37% in 19 extrapancreatic NETs of the GI tract (Spada et al. 2016).

High-grade Neuroendocrine Tumors (NET-G3) and Neuroendocrine Carcinoma (NECs)

Cisplatin plus etoposide is the most extensively studied chemotherapy regimen for poorly differentiated NECs of extrapulmonary origin. In the largest retrospective multicenter study, 252 patients with advanced NEC of the gastroenteropancreatic system were analyzed. In this study, cisplatin plus etoposide and carboplatin plus etoposide showed similar efficacy in terms of ORR, PFS, and OS (Sorbye et al. 2013). In the overall cohort, 2% complete remissions and 29% partial remissions were reported. The tumor control rate was 64% with a median PFS of 4 months and a median overall survival of only 11 months (Sorbye et al. 2013). Early treatment onset is crucial for the outcome. At present, there is no established second-line therapy for NECs, but retrospective studies from single centers indicate some efficacy of Temozolomide alone or in combination with capecitabine ± bevacizumab, of 5-FU intravenously or capecitabine orally, combined with either oxaliplatin or irinotecan (Sorbye et al. 2014).

Response rates with cisplatin-based chemotherapy in NETs G3 (Ki-67 is <55%) are much lower than in NECs and cisplatin/etoposide is not recommended. In these patients, temozolomide, targeted drugs, PRRT in selected cases and streptozotocin-based chemotherapy in the case of pancreatic NETs might be considered (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Pavel et al. 2020).

Adjuvant/Neoadjuvant Therapy

There are no prospective randomized clinical trial to support adjuvant therapy in NETs G1/G2. However, adjuvant therapy with platinum-based chemotherapy can be considered in NECs. Neoadjuvant approaches may be used in borderline or locally advanced PanNECs. However, prospective clinical trials for these clinical conditions are warranted (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) et al. 2018; Pavel et al. 2020).

References

Asa, S.L., Mete, O., Cusimano, M.D. et al. (2021 Sep). Pituitary neuroendocrine tumors: a model for neuroendocrine tumor classification. *Mod Pathol* 34 (9): 1634–1650.

Barat, M., Cottereau, A.S., Kedra, A. et al. (2020). the role of interventional radiology for the treatment of hepatic metastases from neuroendocrine tumor: an updated review. *J Clin Med* 9 (7): 2302.

Begum, N., Hubold, C., Buchmann, I. et al. (2014). Diagnostics and therapy for neuroendocrine neoplasia of an unknown primary - a plea for open exploration. *Zentralbl Chir* 139 (3): 284–291.

Begum, N., Wellner, U., Thorns, C. et al. (2015). CUP syndrome in neuroendocrine neoplasia: analysis of risk factors and impact of surgical intervention. *World J Surg* 39 (6): 1443–1451.

Bellizzi, A.M. (2013 Sep). Assigning site of origin in metastatic neuroendocrine neoplasms: a clinically significant application of diagnostic immunohistochemistry. *Adv Anat Pathol* 20 (5): 285–314.

Bellizzi, A.M. (2020). An algorithmic immunohistochemical approach to define tumor type and assign site of origin. *Adv Anat Pathol* 27 (3): 114–163.

Caplin, M.E., Pavel, M., Ćwikła, J.B. et al. (2014). Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 371 (3): 224–233.

Chen, J.X., Wileyto, E.P., and Soulen, M.C. (2018). Randomized embolization trial for neuroendocrine tumor metastases to the liver (RETNET): study protocol for a randomized controlled trial. *Trials* 19 (1): 390.

Cives, M., Ghayouri, M., Morse, B. et al. (2016). Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. *Endocr Relat Cancer* 23 (9): 759–767.

d'Assignies, G., Fina, P., Bruno, O. et al. (2013). High sensitivity of diffusion-weighted MR imaging for the detection of liver metastases from neuroendocrine tumors: comparison with T2-weighted and dynamic gadolinium-enhanced MR imaging. *Radiology* 268 (2): 390–399.

de Graaf, W., van Lienden, K.P., Dinant, S. et al. (2010). Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg* 14 (2): 369–378.

Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS), Netzwerk Neuroendokrine Tumoren (NeT) e.V. (Patientenvertretung), Bundesorganisation Selbsthilfe NeuroEndokrine Tumoren e.V. (NET-sgh) (Patientenvertretung), Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (DGHO), und Arbeitsgemeinschaft Internistische Onkologie (AIO) der Deutschen Krebsgesellschaft e.V, Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie e.V. (DGAV) et al. (2018). Practice guideline neuroendocrine tumors - AWMF-Reg. 021-27. *Z Gastroenterol* 56 (6): 583–681.

Dilz, L.M., Denecke, T., Steffen, I.G. et al. (2015). Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. *Eur J Cancer* 51 (10): 1253–1262.

Dromain, C., de Baere, T., Baudin, E. et al. (2003). MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *Am J Roentgenol* 180 (1): 121–128.

Dromain, C., de Baere, T., Lumbroso, J. et al. (2005). Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol* 23 (1): 70–78.

Dromain, C., Pavel, M.E., Ruszniewski, P. et al. (2019). Tumor growth rate as a metric of progression, response, and prognosis in pancreatic and intestinal neuroendocrine tumors. *BMC Cancer* 19 (1): 66.

Duan, K. and Mete, O. (2016). Algorithmic approach to neuroendocrine tumors in targeted biopsies: practical applications of immunohistochemical markers. *Cancer Cytopathol* 124 (12): 871–884.

Durante, C., Boukheris, H., Dromain, C. et al. (2009). Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. *Endocr-Relat Cancer* 16 (2): 585–597.

Frilling, A., Clift, A.K., Braat, A. et al. (2019). Radioembolisation with 90Y microspheres for neuroendocrine liver metastases: an institutional case series, systematic review and meta-analysis. *HPB (Oxford)* 21 (7): 773–783.

Frilling, A., Li, J., Malamutmann, E. et al. (2009). Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *Br J Surg* 96 (2): 175–184.

Frilling, A., Modlin, I.M., Kidd, M. et al. (2014). Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 15 (1): e8–21.

Galleberg, R.B., Knigge, U., Tiensuu Janson, E. et al. (2017). Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. *Eur J Surg Oncol* 43 (9): 1682–1689.

Garcia-Carbonero, R., Sorbye, H., Baudin, E. et al. (2016). ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology* 103 (2): 186–194.

Hayoz, R., Vietti-Violi, N., Duran, R. et al. (2020). The combination of hepatobiliary phase with Gd-EOB-DTPA and DWI is highly accurate for the detection and characterization of liver metastases from neuroendocrine tumor. *Eur Radiol* 30 (12): 6593–6602.

Jia, Z. and Wang, W. (2018). Yttrium-90 radioembolization for unresectable metastatic neuroendocrine liver tumor: a systematic review. *Eur J Radiol* 100: 23–29.

King, J., Quinn, R., Glenn, D.M. et al. (2008). Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 113 (5): 921–929.

Kulke, M.H., Hörsch, D., Caplin, M.E. et al. (2017a). Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. *J Clin Oncol* 35 (1): 14–23.

Kulke, M.H., Ruszniewski, P., Van Cutsem, E. et al. (2017b). A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. *Ann Oncol* 28 (6): 1309–1315.

La Rosa, S. and Solcia, E. (2020). New insights into the classification of gastric neuroendocrine tumours, expanding the spectrum of ECL-cell tumours related to hypergastrinaemia. *Histopathology* 77 (6): 862–864.

Luchini, C., Pelosi, G., Scarpa, A. et al. (2021). Neuroendocrine neoplasms of the biliary tree, liver and pancreas: a pathological approach. *Pathologica* 113 (1): 28–38.

Machairas, N., Daskalakis, K., Felekouras, E. et al. (2021). Currently available treatment options for neuroendocrine liver metastases. *Ann Gastroenterol* 34 (2): 130–141.

Maragliano, R., Vanoli, A., Albarello, L. et al. (2015). ACTH-secreting pancreatic neoplasms associated with Cushing syndrome: clinicopathologic study of 11 cases and review of the literature. *Am J Surg Pathol* 39 (3): 374–382.

Mazzaferro, V., Pulvirenti, A., and Coppa, J. (2007). Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 47 (4): 460–466.

Mazzaferro, V., Sposito, C., Coppa, J. et al. (2016). The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. *Am J Transplant* 16 (10): 2892–2902.

Mollazadegan, K., Welin, S., and Crona, J. (2021). Systemic treatment of gastroenteropancreatic neuroendocrine carcinoma. *Curr Treat Options Oncol* 10; 22 (8): 68.

Oberg, K. (2000). Interferon in the management of neuroendocrine GEP-tumors: a review. *Digestion* 62 (Suppl 1): 92–97.

Oberg, K. and Eriksson, B. (1991). The role of interferons in the management of carcinoid tumors. *Acta Oncol* 30 (4): 519–522.

Palazzo, M., Lombard-Bohas, C., Cadiot, G. et al. (2013). Ki67 proliferation index, hepatic tumor load, and pretreatment tumor growth predict the antitumoral efficacy of lanreotide in patients with malignant digestive neuroendocrine tumors. *Eur J Gastroenterol Hepatol* 25 (2): 232–238.

Pavel, M., Gross, D.J., Benavent, M. et al. (2018). Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Relat Cancer* 25 (3): 309–322.

Pavel, M., O'Toole, D., Costa, F. et al. (2016). ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 103 (2): 172–185.

Pavel, M., Oberg, K., Falconi, M. et al. (2020). Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 31 (7): 844–860.

Pavel, M.E., Hainsworth, J.D., Baudin, E. et al. (2011). Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 378 (9808): 2005–2012.

Perrodin, S.F., Renzulli, M.M., Maurer, M.H. et al. (2020). can microwave ablation be an alternative to resection for the treatment of neuroendocrine liver metastases? *Endocr Pract* 26 (4): 378–387.

Ramage, J.K., Ahmed, A., Ardill, J. et al. (2012). Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 61 (1): 6–32.

Raymond, E., Dahan, L., Raoul, J.L. et al. (2011 Feb 10). Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 364 (6): 501–513. doi: 10.1056/NEJMoa1003825. Erratum in: N Engl J Med. 2011;364(11):1082.PMID: 21306237.

Raymond, E., Kulke, M.H., Qin, S. et al. (2018). Efficacy and safety of sunitinib in patients with well-differentiated pancreatic neuroendocrine tumours. *Neuroendocrinology* 107 (3): 237–245.

Riihimäki, M., Hemminki, A., Sundquist, K. et al. (2016). The epidemiology of metastases in neuroendocrine tumors. *Int J Cancer* 139 (12): 2679–2686.

Rindi, G., Mete, O., Uccella, S. et al. (2022). Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol* 33 (1): 115–154.

Rindi, G. and Wiedenmann, B. (2020). Neuroendocrine neoplasia of the gastrointestinal tract revisited: towards precision medicine. *Nat Rev Endocrinol* 16 (10): 590–607.

Rinke, A., Müller, H.H., Schade-Brittinger, C. et al. (2009). Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 27 (28): 4656–4663.

Ronot, M., Cuccioli, F., Dioguardi Burgio, M. et al. (2017). Neuroendocrine liver metastases: vascular patterns on triple-phase MDCT are indicative of primary tumour location. *Eur J Radiol* 89: 156–162.

Sahu, S., Schernthaner, R., Ardon, R. et al. (2017). Imaging biomarkers of tumor response in neuroendocrine liver metastases treated with transarterial chemoembolization: can enhancing tumor burden of the whole liver help predict patient survival? *Radiology* 283 (3): 883–894.

Sorbye, H., Strosberg, J., Baudin, E. et al. (2014). Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer* 120 (18): 2814–2823.

Sorbye, H., Welin, S., Langer, S.W. et al. (2013). Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 24 (1): 152–160.

Spada, F., Antonuzzo, L., Marconcini, R. et al. (2016). Oxaliplatin-based chemotherapy in advanced neuroendocrine tumors: clinical outcomes and preliminary correlation with biological factors. *Neuroendocrinology* 103 (6): 806–814.

Stueven, A.K., Kayser, A., Wetz, C. et al. (2019). Somatostatin analogues in the treatment of neuroendocrine tumors: past, present and future. *Int J Mol Sci* 20 (12): 3049.

Uccella, S., Asa, S.L., and Mete, O. (2021). Metastatic neuroendocrine neoplasms of unknown primary site. In: *The Spectrum of Neuroendocrine Neoplasia* (ed. S.L. Asa, S. La Rosa, and O. Mete), 357–387. Cham: Springer.

Uccella, S., La Rosa, S., Volante, M., and Papotti, M. (2018). Immunohistochemical biomarkers of gastrointestinal, pancreatic, pulmonary, and thymic neuroendocrine neoplasms. *Endocr Pathol* 29 (2): 150–168.

Vauthey, J.N., Chaoui, A., Do, K.A. et al. (2000). Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 127 (5): 512–519.

Venable, E.R., Kerr, S.E., Lopes, M.B.S. et al. (2020). metastases from pituitary carcinomas mimicking visceral well-differentiated neuroendocrine tumors: a series of four cases. *Diagn Pathol* 15 (1): 81.

Volante, M., Brizzi, M.P., Faggiano, A. et al. (2007). Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy. *Mod Pathol* 20 (11): 1172–1182.

Wolin, E.M., Jarzab, B., Eriksson, B. et al. (2015). Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. *Drug Des Devel Ther* 9: 5075–5086.

Yao, J.C., Fazio, N., Singh, S. et al. (2016a). Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 387 (10022): 968–977.

Yao, J.C., Guthrie, K.A., Moran, C. et al. (2017). Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. *J Clin Oncol* 35 (15): 1695–1703.

Yao, J.C., Lombard-Bohas, C., Baudin, E. et al. (2010). Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 28 (1): 69–76.

Yao, J.C., Pavel, M., Lombard-Bohas, C. et al. (2016b). Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study. *J Clin Oncol* 34 (32): 3906–3913.

Yao, J.C., Shah, M.H., Ito, T. et al. (2011). Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 364 (6): 514–523.

The Current State of Molecular Imaging and Theranostics in GEP-NETs

Emil Novruzov, Katalin Mattes-György & Frederik L. Giesel

Introduction

The implementation of non-invasive functional imaging with somatostatin analog-(SSA)-based radiopharmaceuticals especially using hybrid positron emission tomography/computed tomography (PET/CT) and peptide receptor radionuclide therapy (PRRT) has profoundly changed the diagnosis and treatment of NENs and thus enabled the so-called patient-tailored therapy management or precision medicine. The mainstay of this molecular concept is the evaluation of overexpression of somatostatin-receptors (SSTRs) on the surface of neuroendocrine tumor cells, albeit SSTR expression in varying degrees is also observed in normal tissue (Table 9). The SSTRs are G protein-coupled receptors that modulate cellular proliferation and secretion activity. They are bound by natural somatostatin (SST), which belongs to the neuropeptide family and exerts several important modulatory functions in the gastrointestinal tract in addition to the secretion of various hormones (Helgebostad et al. 2022; Park et al. 2021).

The SSTR class consists of 5 subtypes (SSTR 1–5), of which subtype 2 is the predominant subclass in GEP-NENs. The low-grade and well-differentiated GEP-NENs exhibit overexpression of SSTR, while in high-grade and poorly differentiated GEP-NENs SSTR expression decreases significantly, leading to the use of alternative radiopharmaceuticals with different target pathways (Table 10). In addition, functioning GEP-NETs can express peptide receptors besides SSTR, such as glucagon-like peptide-1 receptors (GLP-1R) in insulinomas and secretin receptors in gastrinomas. A thorough understanding of receptor subtype profile with concomitant expression of different peptide receptors, their density and distribution among GEP-NEN subtypes, and their correlation with tumor differentiation grade plays a crucial role in nuclear medicine. A proper timing, combination of radiopharmaceutical use with different molecular targets, and harmonization with conventional imaging modalities are needed to perform work-up for primary staging, therapy response monitoring/restaging, and evaluation of SSTR status for the determination PRRT eligibility (e.g., ^{177}Lu or ^{90}Y–DOTA-labeled peptides) (Hu et al. 2021; Kaewput and Vinjamuri 2022; Reubi 2007).

Here, we discuss the impact of molecular imaging and theranostics on GEP-NENs and hereby provide an overview of the most consensus-based employed and/or FDA/EMA-approved radiopharmaceuticals.

Functional Imaging of Low-grade, Well-differentiated GEP-NETs (G1, G2, and G3 with Ki-67-index < 55%)

SSTR scintigraphy with the so-called Octreoscan® (^{111}In-DTPA-DPhe1-octreotide [^{111}In-pentetreotide]) had been the gold standard for several decades in detection of NETs until the development of novel radiolabeled gamma (γ) and positron emitting somatostatin analogs (agonists). Nowadays, gamma-emitting ^{99m}Tc-labeled SSA (Tektrotyd©) and ^{68}Ga or ^{64}Cu-labeled positron emitting DOTAPET tracers represent the modality of choice for functional imaging in GEP-NETs (G1–G3) (Briganti et al. 2019; Gherghe et al. 2022).

^{99m}Tc-labeled peptides (^{99m}TcEDDA/HYNIC-TOC; Tektrotyd©) exhibit higher sensitivity and better spatial resolution with quantitative assessment in comparison to Octreoscan® and additionally more favorable dosimetry than PET tracers. Given the very favorable physical and practical features of ^{99m}Tc and relatively high diagnostic performance with a sensitivity of 80%, specificity of 92%, PPV of 98%, NPV of 47%, and accuracy of 82%, the Tektrotyd scan represents a very good and cost-effective alternative to PET radiopharmaceuticals in centers or countries that lack suitable nuclear medicine infrastructure, PET equipment or deal with reimbursement issues (Figure 14) (Artiko et al. 2016; Gherghe et al. 2022).

Table 9 Distribution of somatostatin receptors (SSTR) in normal human tissue (adapted from Helgebostad et al. 2022).

Tissue	Localization	Receptor subtype
Lymph nodes	Germinal centers	SSTR2
Peyers patches	Germinal centers	SSTR2
Solitary follicles (colon)	Germinal centers	SSTR 2
Appendix	Germinal centers	SSTR 2
Spleen	Red pulp	SSTR 2–3
Thymus	Medulla	SSTR 1–3
Immune cells:		
Macrophages		SSTR 2
Dendritic cells		SSTR 2
B lymphocytes		SSTR 3
T lymphocytes		SSTR 1–5
Kidneys		SSTR 2 (probable)
Prostate	Smooth muscle	SSTR 2
Thyroid gland	Epithelial cells	SSTR 2
Stomach		SSTR 1–4
Small intestine		SSTR 1, SSTR 5
Liver		SSTR 3
Pancreas	β cells	SSTR 2
	α cells	SSTR 3
	δ cells	SSTR 5
Adrenal glands		SSTR 2

Table 10 Expression of somatostatin receptors in different GEP-NENs (%) (adapted from Hu et al. 2021; Kaewput and Vinjamuri 2022).

	Receptor Subtypes				
Tumor Types	SSTR 1	SSTR 2	SSTR 3	SSTR 4	SSTR 5
All GEP-NENs	68	86	46	93	57
Gastrinoma	30	100	79	83	76
Insulinoma	25–31	13–58	19–78	88	19–78
Glucagonoma	67	100	67	67	67
VIPoma	100	100	100	100	100
Mid-Gut NENs	80	95	65	35	75

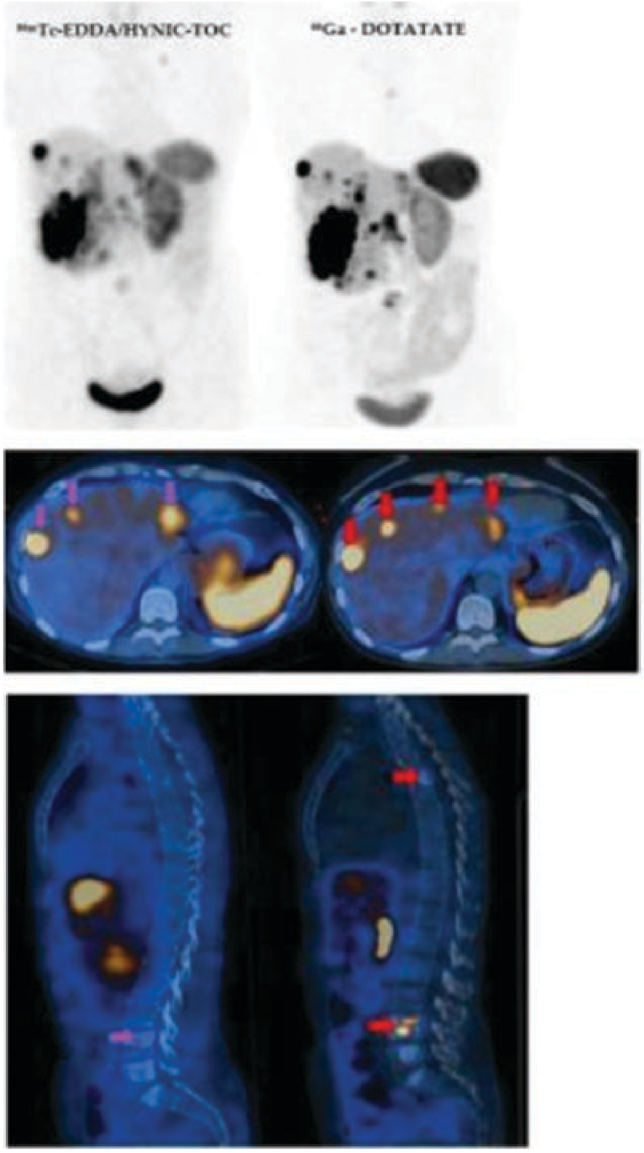

Figure 14 Comparison between ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT (pink arrows) and ^{68}Ga-DOTATATE PET/CT (red arrows) in a 54-year-old female patient, diagnosed with a pancreatic neuroendocrine tumor (G2), with multiple hepatic, lymphatic, and osseous metastases that highlight the better lesion detection rate with ^{68}Ga-DOTATATE PET/CT (adapted from Gherghe et al. 2022).

The DOTA-PET tracers are considered as the current gold standard imaging modality in GEP-NETs due to higher efficiency and spatial resolution than SPECT/CT and scintigraphy (3–6 mm vs. 7–9 mm vs. 10–15 mm, respectively). These tracers are synthesized by the chemical combination of octreotide and a metal radionuclide, namely mostly ^{68}Ga, but also ^{64}Cu using DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) as a chelating agent as in the examples of DOTA-D-Phe-Tyr3-octreotide (DOTATOC), DOTA-1-NaI(3)-octreotide (DOTANOC), or DOTA-D-Phe-Tyr3-octreotate (DOTATATE). These compounds exhibit some minor differences with respect to SSR affinity profile. For example, the DOTATATE shows the most favorable affinity to SSTR 2 and the DOTATOC binds more selectively to SSTR 2 and 5. Nevertheless they can be used interchangeably in clinical practice without any noteworthy diagnostical drawback (Table 11) (Gherghe et al. 2022; Helgebostad et al. 2022).

The ^{68}Ga-labeled SSA PET/CT scan demonstrates a very good diagnostic performance in GEP-NETs with a sensitivity of 90–93% and a specificity of 91–96%. The various meta-analyses report a therapy management change in up to 45% of the patients by using ^{68}Ga-SSA PET/CT with most of the changes involving surgical planning and patient selection for PRRT (Gherghe et al. 2022; Treglia et al. 2021).

Despite the good diagnostic performance and clinical relevance, ^{68}Ga-labeled SSA offer some practical limitations as the requirement of a cost-intensive ^{68}Ge-/^{68}Ga-generator, low activity amounts after single elution, and the short half-life ($t_{1/2:}$ 67.6 minutes) of ^{68}Ga-labeled compounds.

These features narrow the large-scale use of ^{68}Ga-labeled SSA, leading to development of novel radiopharmaceuticals with ^{64}Cu and ^{18}F that show longer half-life and more favorable economic output. The recently introduced ^{64}Cu-DOTATATE and ^{64}Cu-DOTA-TOC demonstrate a better spatial resolution due to lower positron range (0.65 MeV for ^{64}Cu versus 1.90 MeV for ^{68}Gallium). Moreover, the much longer half-life ($t_{1/2}$) with 12.7 hours allows large-scale, economically profitable use without the need for a complicated, expensive nuclear medicine equipment as well as some advantages in imaging techniques such as the acquisition of delayed images in clinical practice. The studies show no significant difference in diagnostic performance on patient basis between ^{68}Ga- and ^{64}Cu-labeled SSA, though in many cases ^{64}Cu-labeled SSA provide much better lesion-to-background contrast and better lesion detection rate (Figure 15). A potential theoretical limitation of the use of ^{64}Cu-labeled SSA, especially in pediatric patients and women of childbearing age, could be the relatively higher radiation dose to the patient than with ^{68}Ga-labeled SSA (at 180–220 MBq 5.7–8.9 mSv vs. at 120–200 MBq 2.8–4.6 mSv) (Johnbeck et al. 2017; Vahidfar et al. 2022).

Another promising novel radiopharmaceutical is the recently introduced PET agent ^{18}F-SiFAlin-TATE (^{18}F-SiFAlin-Glc-Asp2-PEG1-TATE) which exploits the advantages of the radionuclide ^{18}F due its favorable half-life ($t_{1/2}$ 109.7 minutes), low positron energy with a maximum of 0,635 MeV, and the relatively low production costs and wide-availability making it profitable for both large nuclear medicine centers with on-site cyclotron as well as the centers that lack a radiopharmaceutical facility. The preliminary results comparing ^{18}F and ^{68}Ga-labeled SSA demonstrate comparable diagnostic performance with a slightly more favorable lesion-to-background contrast for ^{18}F-SiFAlin-TATE which warrants further investigations with larger trials (Boeck et al. 2020; Ilhan et al. 2020).

Liver metastasis is the most seen organ metastasis with a rate of up to 85% of cases in GEP-NENs and represents the most important prognostic factor for further therapy planning. Given the importance of correct diagnosis of hepatic metastasis, the addition of liver MRI to DOTA-SSA PET/CT has been used in

Table 11 Somatostatin analog affinities (IC_{50}: half maximum inhibitory concentration (the concentration of a drug needed for in vitro inhibition of 50%; the lower the IC50, the stronger the affinity)) (adapted from Hu et al. 2021).

	Affinity (IC_{50} nM) (Mean ± SD)				
Somatostatin analog	**SSTR1**	**SSTR2**	**SSTR3**	**SSTR4**	**SSTR5**
Octreotide	>1000	0.4–2.1	4.4–34.5	>1,000	5.6–32
^{111}In-DTPA-octreotide	>10,000	22 ± 3.6	182 ± 13	>1,000	237 ± 52
^{68}Ga-DOTATOC	>10,000	2.5 ± 0.5	613 ± 140	>1,000	73 ± 21
^{68}Ga-DOTANOC	>10,000	1.9 ± 0.4	40.0 ± 5.8	260 ± 74	7.2 ± 1.6
^{68}Ga-DOTATATE	>10,000	0.20 ± 0.04	>1,000	300 ± 140	377 ± 18
^{90}Y-DOTATOC	>10,000	11 ± 1.7	389 ± 135	>10,000	114 ± 29
^{177}Lu-DOTATATE	>1,000	2.0 ± 0.8	162 ± 16	>1,000	>1,000

GEP-NENs to increase diagnostic accuracy, especially for the patients planned for curative surgery or metastasectomy (Table 12). The novel hybrid imaging method with the combination of PET and MRI, PET/MRI scan, to overcome the practical problems with time-delayed fusion of PET and MRI scans seems to outperform DOTA-SSA PET/CT imaging with up to 15.3% additional sensitivity and higher specificity (95.6–100% for PET/MRI versus 88.2–100% for PET/CT) in the detection of liver metastases, according to the meta-analysis by Choi et al. However, the high cost, long acquisition time as wells as complicated reading are still the limiting factors for widespread use of DOTA-SSA PET/MRI scan (Choi et al. 2022; Hayoz et al. 2020; Hu et al. 2021; Półtorak-Szymczak et al. 2021).

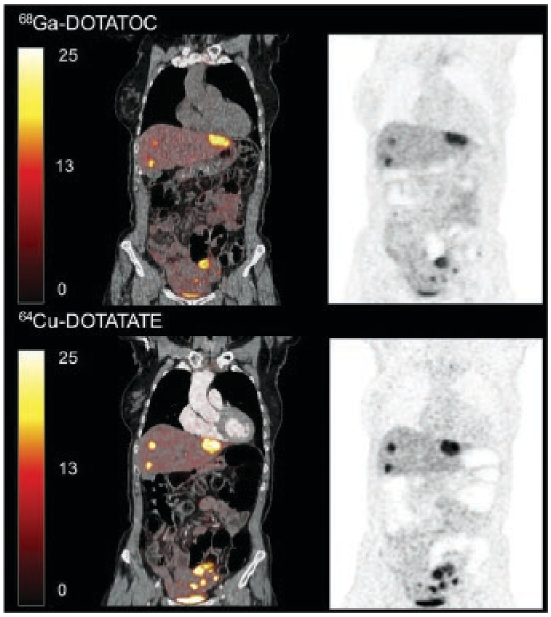

Figure 15 Better detection of NET hepatic metastases and increased number of detected lesions in intestinal region due to better lesion-to-background contrast with 64Cu-DOTATATE than with 68Ga-DOTATOC (adapted from Johnbeck et al. 2017).

As aforementioned (see Table 10), insulinomas demonstrate a relatively low level of SSTR 2 with less than 60% and are usually small-size tumors that escape very often the conventional morphological as well as SSTR imaging. However, these functioning GEP-NET tumors show a very strong overexpression of GLP-1R, which regulates gastric emptying, glucagon secretion, and insulin secretion from pancreatic α- and β-cells, respectively, via binding to GLP. After the introduction of GLP-1R agonist with Exendin-4, the ^{68}Ga-labeled Exendin-4 PET tracer, has become the modality of choice in the diagnostic work-up of patients with endogenous hyperinsulinemic hypoglycemia or culprit lesion localization in benign insulinoma due to high diagnostic performance with a sensitivity of 94% and a specificity of 83% (Leung 2013; Shah et al. 2021; Treglia et al. 2021).

High-grade Neuroendocrine Tumors (G3 with Ki-67-index > 55%) and Neuroendocrine Carcinomas (NECs)

With increasing proliferation activity and dedifferentiation, NENs lose SSTR expression, while these neoplasms exhibit a significant increase in cell glucose metabolism due to the so-called Warburg effect. This is also defined as “flip-flop” phenomenon in GEP-NENs which explains greater SSTR expression and decreased glycolytic activity in well-differentiated tumors, and conversely decreased SSTR expression and greater glycolytic activity in poorly differentiated tumors. The flip-flop phenomenon has been a great challenge in the diagnosis and therapy planning of GEP-NENs that is tried to be overcome with the employment of a number of radiopharmaceuticals (Kaewput and Vinjamuri 2022; Park et al. 2021).

Table 12 The sensitivity of different imaging modalities for pNETs and their metastases in the liver (pNET: Pancreatic Neuroendocrine Tumor; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; US: Ultrasound; EUS: Endoscopic Ultrasound), adapted from Choi et al. (2022), Hu et al. (2021), Półtorak-Szymczak et al. (2021), and Schillaci et al. (2003).

	Sensitivity (%)				
Imaging modality	**Gastrinoma**	**Insulinoma**	**pNET <1.5 cm**	**pNET >2.5 cm**	**Liver metastasis**
CT scan	5–47	20–63	34	50–94	82
MRI	10–44	10–85	34	60–95	90–95
US	0–21	26–50	11–33	30–76	N/A
Angiography	15–51	50–60	30–60	60–90	N/A
EUS	40–63	71–94	40–90	82–100	N/A
^{111}In-pentetreotide (OctreoScan)	30–32	33–60	29–30	52–96	92,4
^{68}Ga-DOTATAC PET/CT	68–100	31–90	60–80	68–100	56,6–93,7
^{68}Ga-DOTATAC PET/MRI	N/A	N/A	N/A	N/A	76,2–100

^{18}F-FDG PET/CT, an ^{18}F-labeled glucose analogue demonstrating increased uptake in malignant cells due to increased cell glucose transporters to enter glycolysis pathway, has been commonly employed in GEP-NETs to predict tumor heterogeneity in relatively low-grade NET or tumor aggressiveness and prognosis in high-grade NETs and NECs. Increased FDG uptake in tumor cells reveals also poor overall survival (OS) as well as progression-free survival (PFS) rates in GEP-NETs irrespective of concomitant SSTR expression. To exploit this phenomenon, the concept of dual tracer imaging by combining FDG and DOTA-SSA PET has been introduced in a complementary manner in order to identify the highest-grade and most aggressive lesions by localizing the highest FDG uptake with a simultaneous lowest DOTA-SSA uptake (FDG positive and SSTR negative lesions). This unique tracer combination outperforms any tissue sampling or biopsy to gain a detailed noninvasive understanding of tumor heterogeneity in the whole body and the likelihood of PRRT response. Besides, tumor transformation during tumor therapy or in follow-up can also be detected via dual tracer imaging, which aids in proper therapy adjustment (Figures 16 and 17). Finally, the clinical indications for dual tracer imaging by combining FDG and DOTA-SSA PET could be summarized as follows (Ambrosini et al. 2021; Carideo et al. 2019; Fine et al. 2022; Park et al. 2021).

a G1/2 NET with mismatched lesions (CT-positive/DOTA-SSA-negative)

b G1/G2 NET at disease progression

c G3 NET with very high proliferative activity (Ki-67-index > 55%) and NEC

d Negative DOTA-SSA imaging in GEP-NET with unknown primary

e Appropriate selection of patients for PRRT

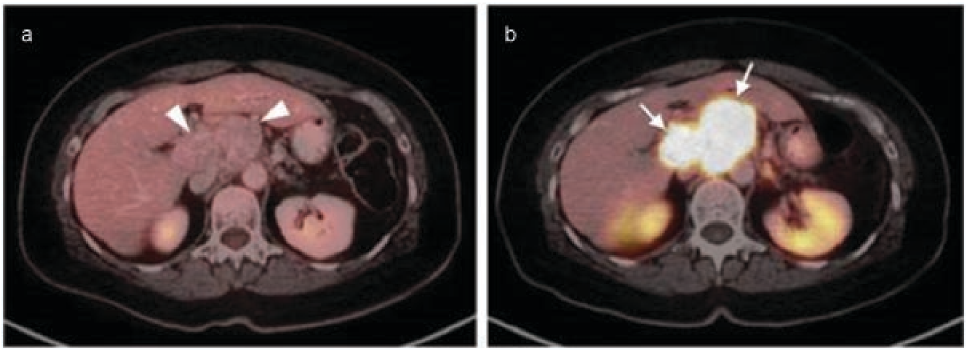

Figure 16 Well-differentiated NET metastasis to caudate lobe of liver and lymph nodes at hepatic hilum in comparison between ^{18}F-FDG PET-CT (a) and ^{68}Ga-DOTA-TATE PET-CT (b). (a) Low metabolic activity on FDG PET-CT (white arrowheads). (b) Intense DOTATATE uptake in the metastatic mass and lymph nodes (white arrows). Adapted from Fine et al. (2022).

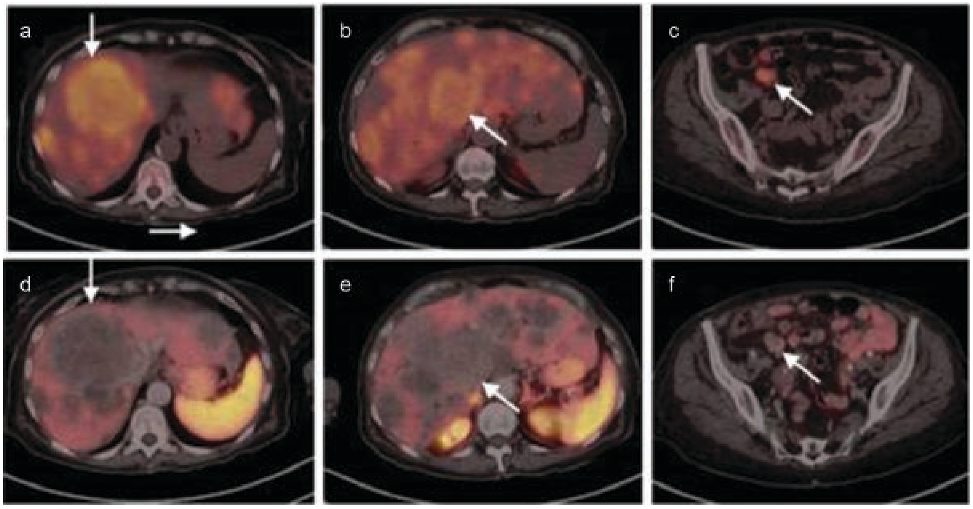

Figure 17 Poorly differentiated NET metastasis to liver and mesenterium in comparison between ^{18}F-FDG PET-CT (a–c) and ^{68}Ga-DOTA-TATE PET-CT (d–f). (a–c), Axial FDG PET-CT images of the abdomen and upper pelvis show a hypermetabolic state of the metastatic masses (white arrow). (d–f) No significant DOTATATE uptake in the metastases (white arrows). Adapted from Fine et al. (2022).

Recently, a novel radiopharmaceutical class, ^{68}Ga-labeled fibroblast activation protein-inhibitor (^{68}Ga-FAPI), with a different molecular target has been introduced that has also potential for radioligand therapy. FAP is overexpressed by cancer-associated fibroblasts in tumor stroma in various epithelial malignancies. The preliminary experience in several case reports indicate substantial uptake of FAPI in low-grade NETs as well as in NECs. Due to theranostic potential, FAPI appears to be very promising, particularly for radioligand therapy in patients with disseminated high-grade NETs and NECs. However, further studies are warranted to fully explore the theranostic potential of FAPI in GEP-NETs (Fortunati et al. 2022).

SSTR-based Peptide-receptor-radioligand Therapy (PRRT) (GEP-NETs G1/2 And G3 with Ki-67 Index < 55%)

Patients with GEP-NETs present usually already in a locally advanced or metastatic state, making a curative surgical therapy largely impossible. The current first-line treatment with SSAs and also second-line systemic therapy options such as palliative radiochemotherapy and everolimus can show symptomatic relief and stabilization of tumor growth for various periods; however, these therapy strategies don't represent a curative approach (Raymond et al. 2021).

Peptide receptor radionuclide therapy (PRRT) is an evolving, highly promising systemic treatment with a curative potential consisting of the administration of a tumor-targeting radiopharmaceutical to the patient in conjunction with the so-called "magic-bullet" concept. This concept foresees the target-specific binding of a certain radiopharmaceutical for on-site retention by being internalized and stored in lysosomes in tumor cells in order to unfold its destructive potential causing DNA-damage and chromosomal aberrations by using alpha- or beta-emitting radioisotopes, while sparing the surrounding cells and tissues. A typical radiopharmaceutical in PRRT of NET consists of a radiation emitting radiometal (e.g. ^{177}Lu or ^{225}Ac), a peptide (e.g. TATE or DOC) which binds to SSTR and a chelating agent (DOTA) that binds the radiometal in a stable manner and allows its conjugation (Figure 18). PRRT represents a significant treatment advance for patients with GEP NETs because of its cytoreductive potential and ability to elicit prolonged disease-progression free periods. In general, low-grade, well-differentiated tumors such as GEP-NETs G1/G2 and, in some cases, high-grade G3 tumors with a Ki-67 index of up to 55% benefit from PPRT, whereas poorly differentiated NETs tumors or NECs do not. The degree of SSTR expression and thus patient selection for PRRT is determined by the current gold-standard diagnostic modality with DOTA-SSA PET tracers. This nuclear diagnostic plays the most important role in clinical

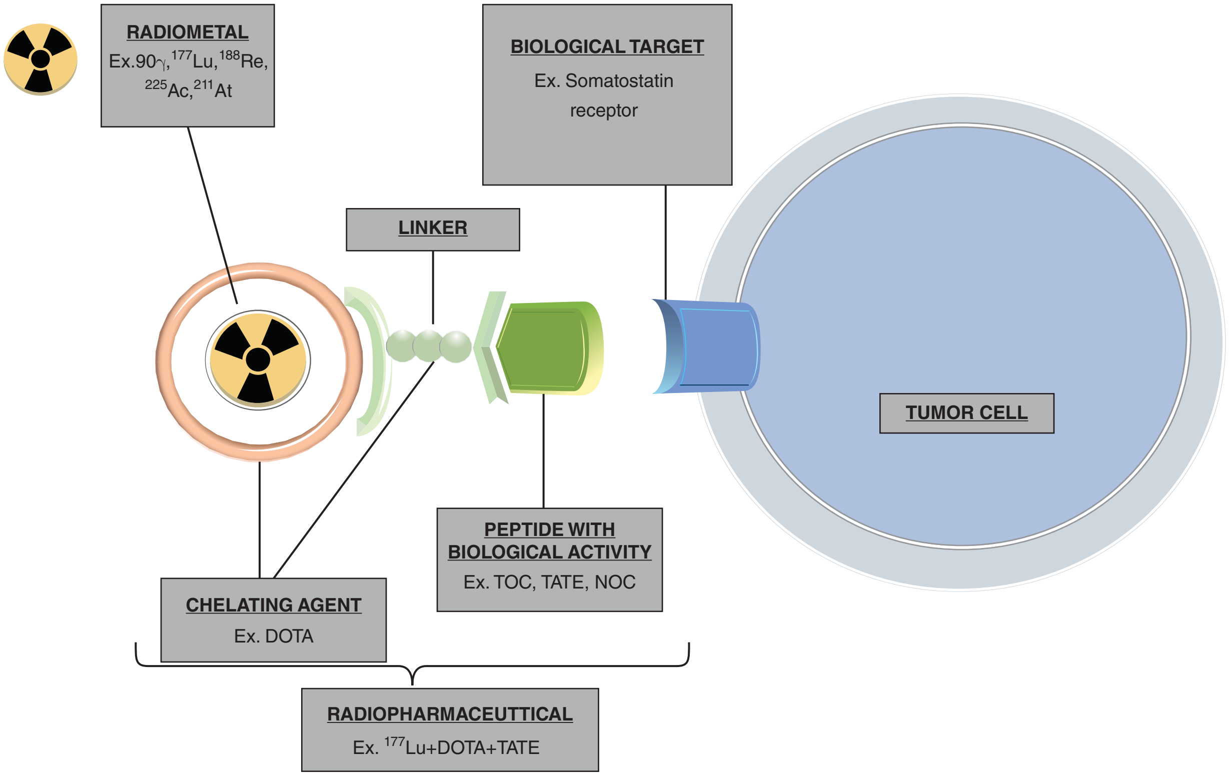

Figure 18 Schematic design of radiopharmaceutical complex (adapted from Del Olmo-García et al. 2022).

decision-making with regard to therapy response monitoring and follow-up alongside FDG imaging, in conjunction with dual tracer concept. This concept aids especially in high-grade or dedifferentiated NETs at initial diagnosis or in the course of therapy the proper patient selection for PRRT or combination therapies of PRRT with other systemic therapy modalities (Del Olmo-García et al. 2022; Raymond et al. 2021).

In theranostic approach, two classes of radiopharmaceuticals, namely α- and β(-)-emitting radiopharmaceuticals, are exploited with different irradiation characteristics that require a basic understanding of the physical principles related to dosimetry (dose–effect relationship), effective treatment range, and toxicity profile in order to plan patient-tailored therapeutic regimens in combination with other systemic therapies or SSAs (Del Olmo-García et al. 2022; Raymond et al. 2021).

α-particles are characterized by high-linear-energy transfer due to the short range of penetration (<100 μm, about 2–3 cell diameters) and apoptosis induction by breaking DNA double strands largely independent of cell cycle and oxygenation status, while minimizing damage to surrounding healthy tissue. Thus, α-emitting radiopharmaceutical emerge as an option particularly for patients who appear to be already refractory to conventional therapies or PRRT with β-emitting radionuclides. Regarding PRRT, among numerous α-emitting radionuclides, ^{225}Ac and ^{213}Bi have been employed in clinical use due to more favorable half-life and ability to incorporate them chemically and stably into a suitable vector. On the other hand, β-emitting radionuclides have a much larger, low-energy irradiation range (12 mm for ^{90}Y and 2 mm for ^{177}Lu) causing single-strand DNA breaks with less lethality. Collateral damages can limit its clinical use due to relatively higher toxicity profile to the kidneys and bone marrow (Figure 19) (Kratochwil et al. 2014; Kunikowska & Królicki 2020).

Targeted Beta Therapy

For targeted beta therapy in GEP-NETs, the beta emitting radionuclides ^{90}Y (^{90}Y-DOTA0-Tyr3–octreotide (^{90}Y-DOTATOC)) and ^{177}Lu had been widely investigated until ^{177}Lu-DOTATATE achieved a breakthrough in PRRT of NETs by FDA and EMA approval (Lutathera®) due to very promising results from open, randomized, controlled phase-III-trial (NETTER-1-Study) in 2017. ^{90}Y emits β-particles with high maximum energy ([Emax] 2.27 MeV) and a long maximum particle range (10 mm) with a half-life of 2.7 days, whereas ^{177}Lu has lower energy ([Emax] 0.497 MeV) and a shorter particle range (2 mm) with a half-life of 6.7 days. Besides, ^{177}Lu emits gamma radiation allowing dosimetry of actual absorbed dose of tumors and organs at risk, such as the kidneys, on a patient-specific basis. Although the high-energy, long-range beta emitter ^{90}Y initially appeared to have a favorable treatment response in 10–34% of patients and also advantages in treating large tumor foci, the relatively high toxicity profile with nephrotoxicity with very increased rates of end-stage renal disease coupled with a good toxicity profile of ^{177}Lu with encouraging clinical results has led to a shift in research direction (Del Olmo-García et al. 2022; Kunikowska and Targeted 2020).

The NETTER-1 trial demonstrated a significant improvement of PFS in the PRRT/SSA combination arm compared to only

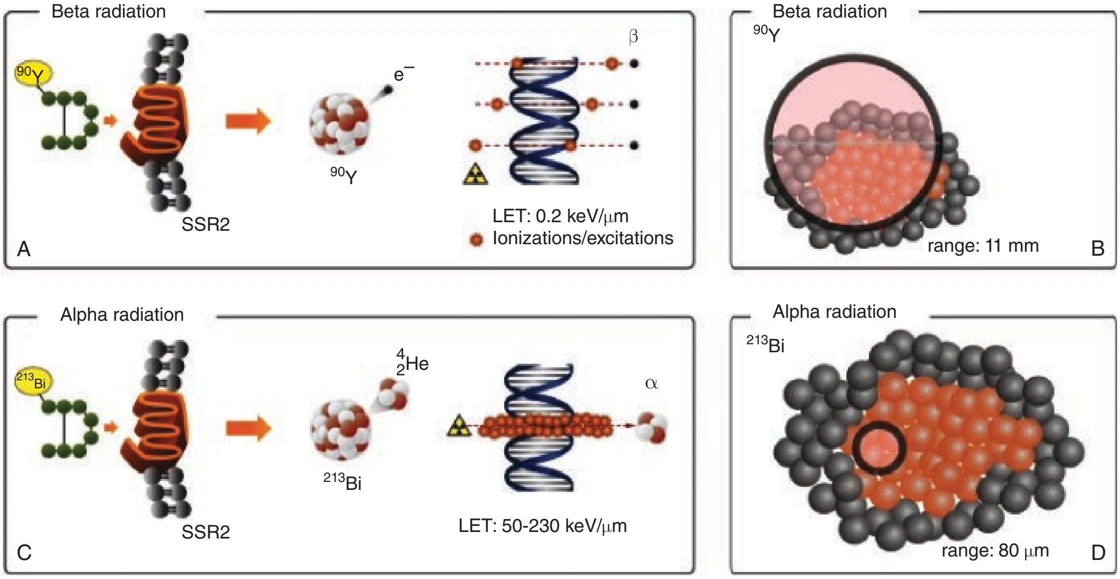

Figure 19 Comparison of alpha and beta emitters after binding of the radionuclide-labeled octreotide analogue DOTATOC to the somatostatin receptor subtype-2 (SSR2): **c, d**: the emitted alpha particle causes high-density ionization effects, resulting mainly in double-strand DNA breaks in a tissue range of approximately two cell diameters and thus resulting in less cross-fire" of surrounding normal tissue. **a, b**: In contrast, the beta particles cause repairable single-strand DNA damage with a mean tissue range of (3 mm) approximately 75 cell diameters (adapted from Kratochwil et al. 2014).

SSA arm (PFS 40 months vs. 8.4 months) as well as an excellent improvement of quality of life evaluated by quality-of-life deterioration (28.8 months for PRRT-Lu vs. 6.1 months with SSA). Luthatera therapy exhibits a disease control rate of approximately 80% in advanced or metastatic, non-operable GEP-NETs (Kratochwil et al. 2014). Since the implementation of Luthatera use in clinical setting a lot of efforts have been made to generate evidence-based data regarding determination of clinical indications and contraindication with respect to potentially limiting factors of nephrotoxicity and bone marrow suppression, the sequencing of PRRT among other systemic, second-line therapy modalities, and also developing strategies to increase the tumor sensitivity to PRRT, particularly in heterogenous tumors with suboptimal SRRT expression (Del Olmo-García et al. 2022).

PRRT, particularly Luthatera, should be considered as a treatment option for advanced SSTR-positive NETs in the context of prior consensus-based multidisciplinary discussion. The main eligibility for PRRT in GEP-NETs is the correct assessment of overexpression of SSTR by the tumor cells, which is currently evaluated on DOTA-PET tracer scan by either the modified Krenning Score (3 or higher), which visually assesses SRRT level by comparing tumor uptake with spleen and liver uptake or more precisely by the semiquantitative assessment via SUV_{max} measurement (cut-off SUV_{max} value: >16,4) and determination of tumor-to-liver ratio (cut-off T/L ratio > 2,2). In addition, malignant insulinomas usually retain SSTR overexpression while losing GLP-1R expression, also making them eligible for PRRT. The multidisciplinary EANM Focus 3 panel recommends PRRT as a second-line treatment for gastrointestinal NETs with ^{68}Ga-DOTA-SSA uptake in all lesions

- in G1/G2 NET at disease progression
- in a subset of G3 NET with Ki-67 index < 55% provided all lesions are positive at 18F-FDG and 68Ga-DOTA-SSA
- PRRT as a first line of treatment in non-resectable or disseminated NETs in a minority of highly selected patients with high SSTR expression (based on risk and symptoms, primary tumor location)
- PRRT rechallenge may be used for in patients with stable disease for at least one year after therapy completion (Ambrosini et al. 2021; Kratochwil and Giesel 2014; Kratochwil et al. 2015)

Despite various, mostly only mild to moderate, short- and long-term side effects, there is not any absolute contraindication for PRRT. However, a systematic patient evaluation with respect to clinical details, tumor histopathologic findings, laboratory values and a summed interpretation on a multidisciplinary basis ensures proper patient selection and prediction of potential adverse effects and complications in advance of therapy. As an orientation in clinical setting, the laboratory values outlined in Table 13 could be taken as a reference point before Luthatera therapy is started. Luthatera therapy involves the intravenous administration of an activity of 7.4 GBq (200 mCi) every 8 ± 1 week for 4 cycles with a subsequent DOTA-SSA PET/CT scan 3 months after therapy completion for therapy response monitoring (Figure 20) (Hendifar et al. 2022; Hope et al. 2019).

As aforementioned, particularly for the high-volume or heterogenous NETs with even suboptimal SSTR expression, newly emerged, alternative therapies (Tandem Therapy) with combination of the high-energy emitting, widely penetrating ^{90}Y-DOTATOC for targeting lesions with a larger size and/or heterogeneity and the medium-energy, shortly penetrating

Table 13 Recommended laboratory thresholds for PRRT treatment (adapted from Hope et al. 2019).

Laboratory value	Recommended laboratory value
Hemoglobin	>8 g/dL
White blood cell count	>2 K/mm^3
Platelet count	>70 K/mm^3
Estimated glomerular filtration rate	>50 mL/min
Total bilirubin	≤ 3 × ULN
Serum albumin	>3,0 g/dl

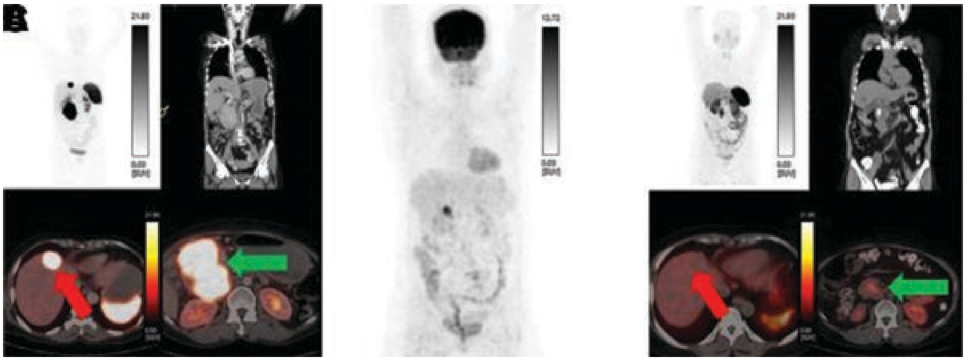

Figure 20 Luthatera treatment workflow. Intravenous amino acids for nephroprotection are given 30 minutes before ^{177}Lu-DOTATATE and continue during and for approx. 3 hours after treatment. The first therapy response control with DOTA-SSA PET/CT scan is performed no earlier than 3 months after completion of therapy in order to overcome early post-therapeutic, temporary pseudoprogression of tumor lesions (adapted from Hendifar et al. 2022).

^{177}Lu-DOTATATE for targeting smaller lesions may represent an option. Various studies report very promising results with this concept, indicating the synergistic effect of two beta-PRRT. Another promising concept is the addition of radiosensitizing chemotherapy such as 5-fluorouracil (5-FU), capecitabine or temozolomide (CAPTEM) to beta-PRRT to increase the toxicity and thus increase the tumor response rate (Ahmadi Bidakhvidi et al. 2021).

In summary, Luthatera has changed the landscape in the PRRT of GEP-NETs. However, because of the inevitable multidisciplinarity of clinical decision making, need of dedicated nuclear medicine facilities, regulatory and reimbursement issues, this therapy is reserved to high-end, high-volume medical centers.

Targeted Alpha Therapy

High-energy, low-range α-emitting radiopharmaceuticals containing ^{213}Bi-DOTATOC were first developed and used in clinical practice by the Heidelberg research group in a cohort of 25 patients with advanced neuroendocrine tumors who were refractory to both conventional therapy and β-emitting PRRT. ^{213}Bi is a mixed alpha/beta emitter with a half-life of 46 min and decays mainly via beta- emission to the ultra-short-lived, pure alpha emitter with a branching ratio of 97.8%, which is also mainly responsible for the cytotoxic effects. ^{213}Bi-DOTATOC was administered in increasing activities in cycles every 2 months (first cycle, about 1.0 GBq; second cycle, about 1.5 GBq; third cycle, 2–4 GBq; fourth cycle, as available from the generator system). Additionally, the patients received a nephroprotective solution (1000 ml of a nephroprotective solution containing 30 g lysine, 30 g arginine, and 500 ml of Gelofusine followed by 1000 ml of saline) to prevent renal toxicity. Given renal toxicity and bone marrow suppression have been considered as potential limiting factors for PRRT, the follow-up of patients demonstrated no significantly increased long-term complications. In this pioneering study, the researchers could demonstrate the feasibility and potential of alpha-emitting radionuclides with ^{213}Bi-DOTATOC for long-lasting disease remission in otherwise therapy refractory patients (Figure 21) (Kratochwil and Giesel 2014; Kunikowska and Targeted 2020; Morgenstern et al. 2018).

In the wake of the initial promising results with ^{213}Bi-DOTATOC, Kratochwil et al. investigated also ^{225}Ac-DOTATOC and evaluated the dose-dependent toxicity profile in terms of single cycle versus fractionation concept and clinical follow-up in a cohort of 34 patients with a total of 46 therapy cycles in a 5-year-period. ^{225}Ac has a long half-life with 9.9 days and decays via a cascade of six short-lived radionuclide daughters to near stable ^{209}Bi ($T_{1/2}$ = 1.9 × 1019 y). They could determine maximum tolerable dose (MTD) with a reasonable level of long-term renal and hematological complications, which involved either the administration of approx. 20 MBq per cycle with 4 monthly repetitions up to a cumulative dose of 80 MBq or 40 MBq as a single tolerable dose. The investigators subsequently observed long-lasting tumor response in the patients in the following period (Figure 22); however, an efficacy analysis regarding the determination of a tolerable treatment regimen with concurrent evidence of tumor response could not be conducted due to the relatively small and heterogenous patient cohort (Delpassand et al. 2022; Morgenstern et al. 2018). Recently, Delpassand et al. conducted the phase-1 dose-escalation clinical study of ^{212}Pb-DOTAMTATE in 10 patients with advanced metastatic NETs. The patients were intravenously administered with 4 cycles of 2.50 MBq/kg (67.6 µCi/kg) of ^{212}Pb-DOTAMTATE administered at 8-week intervals which demonstrated an overall response rate of 80% with very good toxicity profile. These results are exciting not only because of the highly promising tumor response rates but also very favorable physical characteristics of ^{212}Pb. This radionuclide is a β-emitter ($T_{1/2}$ = 10.64 h) and belongs to the distinct group of the so-called in vivo generators, which generate the required alpha-emitting daughter nuclide, namely ^{212}Bi ($T_{1/2}$ = 1 h), after administration into the patient. The radionuclide ^{212}Pb belongs to a radioactive series of long-lived parent ^{228}Th ($T_{1/2}$ = 1.9 year) (Figure 23) (Delpassand et al. 2022; Kokov et al. 2022).

Although the alpha-emitting radiopharmaceuticals in PRRT are highly exciting therapeutic options, the main limiting factor

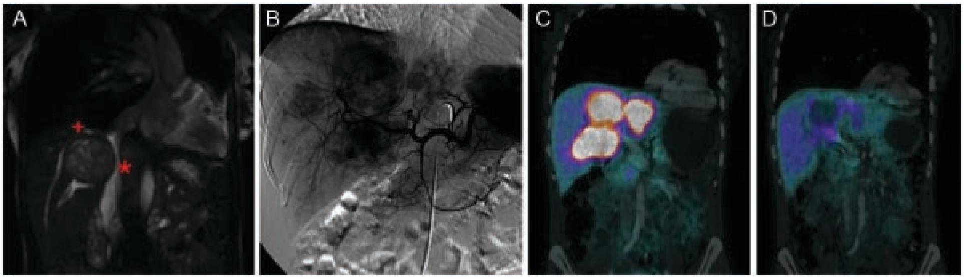

Figure 21 A large hepatic mass with the acute danger of occlusion of both the liver veins and the lower cava vein is treated by direct injection of α-emitting ^{213}Bi-DOTATOC via proper hepatic artery. a) MR image b) digital subtraction angiogram c) PET/CT image showing intense pre-therapeutic ^{68}Ga-DOTATOC uptake d) PET/CT image 6 months after therapy showing fully remission without any ^{68}Ga-DOTATOC uptake in the residual tumor (adapted from Kratochwil et al. 2014).

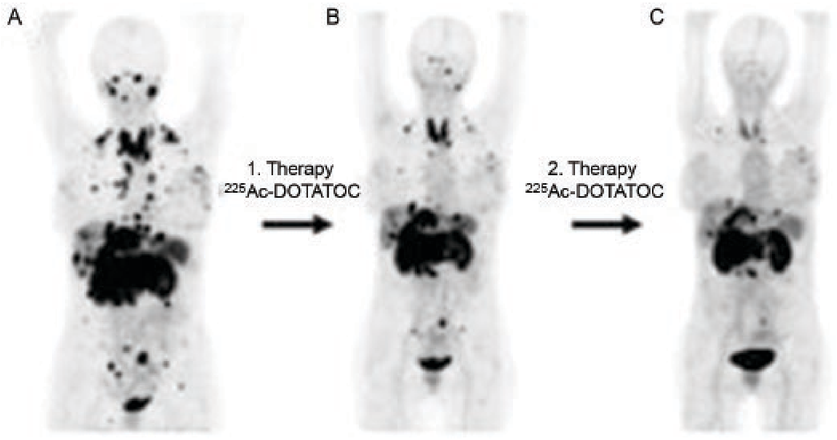

Figure 22 Therapy response monitoring with ^{68}Ga-DOTATOC PET/CT images in a patient with therapy refractory NET showing partial response after two treatment cycles with 16 MBq (1st cycle) and 42 MBq (2nd cycle) ^{225}Ac-DOTATOC. (A): before therapy (B): 4 months after first therapy with 16 MBq ^{225}Ac-DOTATOC (C): 3 months after second therapy with 42 MBq ^{225}Ac-DOTATOC (adapted from Morgenstern et al. 2018).

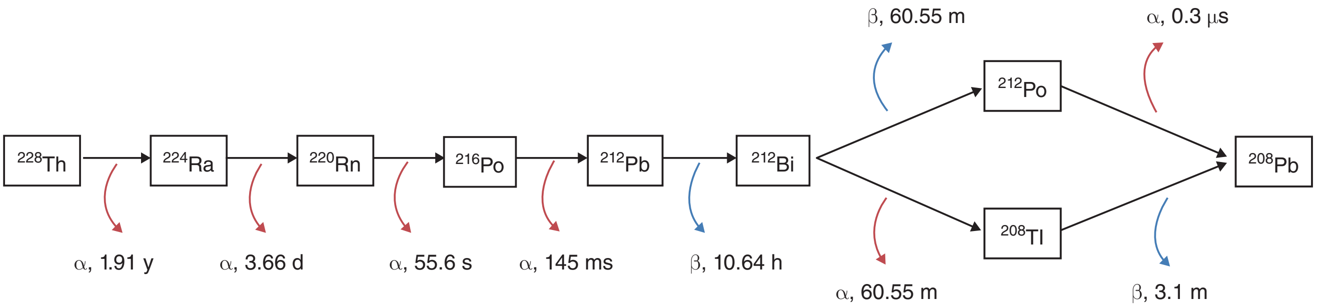

Figure 23 ^{228}Th decay chain scheme (adapted from Kokov et al. 2022).

for the wide research and clinical use is the limited availability with the current worldwide production of ^{225}Ac with just 68 GBq/year. Alternative, commercially promising production ways such as accelerator-based routes have not been implemented, yet. Nevertheless, the recently introduced radiopharmaceutical ^{212}Pb-DOTAMTATE could overcome the current disadvantages of the other alpha-emitting radiopharmaceutical. Altogether, α-emitters appear to be very important and highly promising therapeutic option, especially for systemic therapy and beta-PRRT refractory patients and thus warrants further research regarding more effective radionuclide production as well as establishing evidence-based protocols and guidelines (Delpassand et al. 2022; Morgenstern et al. 2018).

References

Ahmadi Bidakhvidi, N., Goffin, K., Dekervel, J. et al. (2021). Peptide receptor radionuclide therapy targeting the somatostatin receptor: basic principles, clinical applications and optimization strategies. *Cancers (Basel)* 14 (1): 129.

Ambrosini, V., Kunikowska, J., Baudin, E. et al. (2021). Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. *Eur J Cancer* 146: 56–73.

Artiko, V., Afgan, A., Petrović, J. et al. (2016). Evaluation of neuroendocrine tumors with 99mTc-EDDA/HYNIC TOC. *Nucl Med Rev* 19: 99–103.

Boeck, S., Unterrainer, M., Gildehaus, F.J. et al. (2020). Biodistribution and first clinical results of 18F-SiFAlin-TATE PET: a novel 18F-labeled somatostatin analog for imaging of neuroendocrine tumors. *Eur J Nucl Med Mol Imaging* 47 (4): 870–880.

Briganti, V., Cuccurullo, V., Di Stasio, G.D., and Mansi, L. (2019). Gamma emitters in pancreatic endocrine tumors imaging in the PET era: is there a clinical space for 99mTc-peptides? *Curr Radiopharm* 12 (2): 156–170.

Carideo, L., Prosperi, D., Panzuto, F. et al. (2019). Role of combined [68Ga]Ga-DOTA-SST analogues and [18F]FDG PET/CT in the management of GEP-NENs: a systematic review. *J Clin Med* 8 (7): 1032.

Choi, S.J., Choi, S.H., Lee, D.Y. et al. (2022). Diagnostic value of [68 Ga]Ga-DOTA-labeled-somatostatin analogue PET/MRI for detecting liver metastasis in patients with neuroendocrine tumors: a systematic review and meta-analysis. *Eur Radiol* 32 (7): 4628–4637.

Del Olmo-García, M.I., Prado-Wohlwend, S., Bello, P. et al. (2022). Peptide receptor radionuclide therapy with [177Lu]Lu-DOTA-TATE in Patients with advanced GEP NENs: present and future directions. *Cancers (Basel)* 14 (3): 584.

Delpassand, E.S., Tworowska, I., Esfandiari, R. et al. (2022). Targeted alpha-emitter therapy with 212Pb-DOTAMTATE for the treatment of metastatic SSTR-Expressing neuroendocrine tumors: first-in-human, dose-escalation clinical trial. *J Nucl Med* 63 (9): 1326–1333.

Fine, G.C., Covington, M.F., Koppula, B.R. et al. (2022). Morton KA. PET-CT in clinical adult oncology-vi. primary cutaneous cancer, sarcomas and neuroendocrine tumors. *Cancers (Basel)* 14 (12): 2835.

Fortunati, E., Argalia, G., Zanoni, L. et al. (2022). PET radiotracers for the imaging of neuroendocrine neoplasms. *Curr Treat Options Oncol* 23 (5): 703–720.

Gherghe, M., Lazăr, A.M., Stanciu, A.E. et al. (2022). The new radiolabeled peptide 99mTcEDDA/HYNIC-TOC: is it a feasible choice for diagnosing gastroenteropancreatic NETs? *Cancers (Basel)* 14 (11): 2725.

Hayoz, R., Vietti-Violi, N., Duran, R. et al. (2020). The combination of hepatobiliary phase with Gd-EOB-DTPA and DWI is highly accurate for the detection and characterization of liver metastases from neuroendocrine tumor. *Eur Radiol* 30 (12): 6593–6602.

Helgebostad, R., Revheim, M.E., Johnsrud, K. et al. (2022). Clinical applications of somatostatin receptor (agonist) PET tracers beyond neuroendocrine tumors. *Diagnostics (Basel)* 12 (2): 528.

Hendifar, A.E., Mehr, S.H., and McHaffie, D.R. (2022). Best practices for the coordinated care of patients with neuroendocrine tumors undergoing peptide receptor radionuclide therapy. *Pancreas* 51 (3): 213–218.

Hope, T.A., Abbott, A., Colucci, K. et al. (2019). NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with 177Lu-DOTATATE. *J Nucl Med* 60 (7): 937–943.

Hu, Y., Ye, Z., Wang, F. et al. (2021 May 19). Role of somatostatin receptor in pancreatic neuroendocrine tumor development, diagnosis, and therapy. *Front Endocrinol (Lausanne)* 12: 679000.

Ilhan, H., Lindner, S., Todica, A. et al. (2020). Biodistribution and first clinical results of 18F-SiFAlin-TATE PET: a novel 18F-labeled somatostatin analog for imaging of neuroendocrine tumors. *Eur J Nucl Med Mol Imaging* 47 (4): 870–880.

Johnbeck, C.B., Knigge, U., Loft, A. et al. (2017). Head-to-head comparison of 64Cu-DOTATATE and 68Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors. *J Nucl Med* 58 (3): 451–457.

Kaewput, C. and Vinjamuri, S. (2022). Role of Combined 68Ga DOTA-Peptides and 18F FDG PET/CT in the evaluation of gastroenteropancreatic neuroendocrine neoplasms. *Diagnostics (Basel)* 12 (2): 280.

Kokov, K.V., Egorova, B.V., German, M.N. et al. (2022). 212Pb: production approaches and targeted therapy applications. *Pharmaceutics* 14 (1): 189.

Kratochwil, C. and Giesel, F.L. (2014). Nuklearmedizinische Therapie endokriner Tumoren [Radionuclide therapy of endocrine-related cancer]. *Radiologe* 54 (10): 1007–1015.

Kratochwil, C., Giesel, F.L., Bruchertseifer, F. et al. (2014). ^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. *Eur J Nucl Med Mol Imaging* 41 (11): 2106–2119.

Kratochwil, C., Stefanova, M., Mavriopoulou, E. et al. (2015). SUV of [68Ga]DOTATOC-PET/CT predicts response probability of PRRT in neuroendocrine tumors. *Mol Imaging Biol* 17 (3): 313–318.

Kunikowska, J. and Targeted, K.L. (2020). α-emitter therapy of neuroendocrine tumors. *Semin Nucl Med* 50 (2): 171–176.

Leung, K. (2013 Feb 18). 18F-Tetrazine-trans-cyclooctene-Cys40-exendin-4. In: *Molecular Imaging and Contrast Agent Database (MICAD)* [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004–2013. (updated 2013 Apr 25).

Morgenstern, A., Apostolidis, C., Kratochwil, C. et al. (2018). An Overview of targeted alpha therapy with 225Actinium and 213Bismuth. *Curr Radiopharm* 11 (3): 200–208.

Park, S., Parihar, A.S., Bodei, L. et al. (2021). Somatostatin receptor imaging and theranostics: current practice and future prospects. *J Nucl Med* 62 (10): 1323–1329.

Półtorak-Szymczak, G., Budlewski, T., Furmanek, M.I. et al. (2021). Radiological imaging of gastro-entero-pancreatic neuroendocrine tumors. the review of current literature emphasizing the diagnostic value of chosen imaging methods. *Front Oncol* 11: 670233.

Raymond, L.M., Korzun, T., Kardosh, A. et al. (2021). The state of peptide receptor radionuclide therapy and its sequencing among current therapeutic options for gastroenteropancreatic neuroendocrine tumors. *Neuroendocrinology* 111 (11): 1086–1098.

Reubi, J.C. (2007). Peptide receptor expression in GEP-NET. *Virchows Arch* 451 (Suppl 1): S47–50.

Schillaci, O., Spanu, A., Scopinaro, F. et al. (2003). Somatostatin receptor scintigraphy in liver metastasis detection from gastroenteropancreatic neuroendocrine tumors. *J Nucl Med* 44 (3): 359–368.

Shah, R., Garg, R., Majmundar, M. et al. (2021). Exendin-4-based imaging in insulinoma localization: systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 95 (2): 354–364.

Treglia, G., Sadeghi, R., Giovinazzo, F. et al. (2021). PET with different radiopharmaceuticals in neuroendocrine neoplasms: an umbrella review of published meta-analyses. *Cancers (Basel)* 13 (20): 5172.

Vahidfar, N., Farzanehfar, S., Abbasi, M. et al. (2022). Diagnostic value of radiolabelled somatostatin analogues for neuroendocrine tumour diagnosis: the benefits and drawbacks of [64Cu]Cu-DOTA-TOC. *Cancers (Basel)* 14 (8): 1914.

GEP-NENs and Hereditary Syndromes

Pietro Antonini, Antonio Pea, Alessandra Pulvirenti & Claudio Luchini

Introduction

While the majority of gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) is considered to be sporadic, around 20% occur in the context of a genetic syndrome. The most frequent of such syndromes are: i) the multiple endocrine neoplasia type 1 (MEN1), ii) the von Hippel–Lindau syndrome (VHL), and iii) the neurofibromatosis type 1 (NF1).

Other "secondary" syndromes that are associated with an increased risk of developing GEP-NENs are: the multiple endocrine neoplasia type 2A, 2B, and 4 (MEN2A, MEN2B, and MEN4), the hereditary paraganglioma (PGL)-pheochromocytoma (PCC) syndrome, the polycythemia-paraganglioma syndrome, the so-called tuberous scleroses complex, the hyperparathyroidism-jaw tumor syndrome (HPT-JT), and the hereditary/familial small intestine neuroendocrine neoplasms syndrome (the most important have been summarized in Table 14). Additional susceptibility genes associated with a smaller fraction of NENs have also been identified, and at least

Table 14 Summarizing table of the most important "secondary" syndromes associated with an increased risk of developing GEP-NENs.

	TSC	MEN 2	MEN 4	Hereditary PGL-PCC syndromes	Her SiNEN
Gene/ Product	TSC1 (hamartin)/ TSC2 (tuberin)	RET	CDKN1B (p27)	Succinate dehydrogenase (SDH)	IPMK, MUTYH, OGG1, cr18 copy loss
Function	Tumor suppressor genes	Tyrosine kinase receptor	Cell cycle regulator	mitochondrial-respiratory chain (complex II) and Krebs cycle	Different functions
Inheritance	Aut dom (2/3 de novo)	Aut dom	Aut dom	Aut dom	Aut dom
Prevalence	1:10.000	1:35.000	0,02-0,2:1000	NA	NA
Type of NENs	Pancreatic insulinoma	MTC, and other rarer NENs	Gastric, pancreatic and bronchial NET, gastrinoma	PGL, PCC	Pancreatic, small intestine NET

Abbreviations: GEP-NEN: gastro-enteropancreatic neuroendocrine neoplasms; TSC: tuberous sclerosis; MEN: multiple neuroendocrine neoplasia; PGL: paraganglioma; PCC: pheocromocytoma; Her SiNEN: hereditary small intestinal neuroendocrine neoplasia; Aut dom: autosomal dominant; NA: not available; MTC: medullary thyroid carcinoma; NET: neuroendocrine tumor.

24 genes have been implicated as potential drivers of neuroendocrine tumorigenesis.

Although in current times knowing the specific mutations of a given NEN has not always immediate implications in terms of precision oncology and tailored treatments, genomic profiling of hereditary GEP-NENs will be included in future algorithms for diagnostics, prognostics, and therapeutic decisions. The recognition of the genetic susceptibility, however, has already provided essential information for guiding genetic counseling and giving the best preventive care, including screening strategies (Crona and Skogseid 2016).

The Multiple Endocrine Neoplasia Type 1 Syndrome (MEN1)

Epidemiology, Molecular Biology, and Clinical Presentation

MEN1 is one of the first described autosomal dominantly inherited complex endocrine syndromes. It shows a prevalence of 2–5:100, 000 individuals and is usually caused by alterations of the *MEN1* gene. The proportion of MEN1 patients with a causative *MEN1* mutation is estimated at up to 95% of patients (Thakker 2014).

MEN1 gene is located on chromosome 11q and encodes for the menin protein, which is a scaffold protein with more than 40 interacting targets, including molecules and cofactors. Thus, it is involved in several biological functions, such as chromatin remodeling, DNA repair and transcription, cell division, protein degradation, cellular motility, and cell-to-cell adhesion (Agarwal 2013). Recently, alternative genes giving rise to MEN1-resembling syndromes have been suggested, such as germline *CDKN1B* (p27kip) mutations resulting in the so-called MEN4 syndrome (Francis et al. 2013).

Of note, a reliable genotype–phenotype correlation cannot be established, since different tumor combinations have been described in members of the same family carrying the same *MEN1* germline variant, or even in identical twins. The MEN-1 syndrome exhibits a high degree of penetrance, but at the same time, it can show a considerable phenotypic variability (Pellegata et al. 2006). The mean age of presentation of MEN1 is around mid-30s, although rare cases of childhood tumors have been reported; the gender distribution is very similar.

Most frequently, MEN1 patients develop tumors in the parathyroid glands (95%), the anterior pituitary gland (20–40%), and in the endocrine cells of the pancreas/duodenum (40–80%). Any of these neoplasms can represent the first lesion. MEN-1-associated GEP-NENs are most commonly gastrinomas (including duodenal gastrinomas) and nonfunctioning neuroendocrine pancreatic tumors; they are generally multifocal and slow-growing lesions. Pancreatic insulinomas can arise in up to 20% of MEN1 patients (Brandi et al. 2001). Also, gastric ECLomas may be encountered (Fujii et al. 1999).

Gastrinomas usually cause abdominal pain, diarrhea, gastroesophageal reflux disease symptoms and peptic ulcers (Zollinger-Ellison Syndrome). Hypergastrinemia is also associated with gastric enterochromaffin-like (ECL)-cell hyperplasia/tumors. Pancreatic insulinomas are characterized by episodic hyperinsulinemia leading to symptomatic hypoglycemia. Regarding the prognosis of MEN1-associated tumors, the most lethal are pancreatic and the thymic NENs, which can develop distant metastases in up to 40% of cases.

The diagnosis of MEN-1 should be based on the occurrence of NENs in two of its three main sites (parathyroid gland, pituitary gland, pancreas/duodenum), or on the occurrence of a NEN in one of the three main sites in a first-degree relative of a MEN-1 patient, or also on the demonstration of a pathogenic and germline *MEN1* mutation in an asymptomatic individual (Turner et al. 2010).

Imaging

Imaging is fundamental in the preoperative settings for the localization of a primary NEN (symptomatic and incidentalomas), as well as for radiological based staging, and also for the restaging during and after treatment. The sensitivity of imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and endoscopic ultrasonography (EUS) for identifying GEP-NENs is very high. "Molecular" imaging includes somatostatin receptor imaging with 68Ga-DOTA-labeled somatostatin analogues (SSA) positron emitter tomography (PET)/CT, high metabolism imaging with 18-fluoro-deoxy-glucose (FDG) PET/CT scanning, and neuroamine synthesis 18F-dihydroxyphenylalanine (DOPA) PET/CT (Casey et al. 2017; Kann et al. 2006; Kornaczewski Jackson et al. 2017; Sundin et al. 2017; van Asselt et al. 2015).

Macroscopy

Grossly, MEN1-associated NENs are indistinguishable from their sporadic counterparts, appearing as brownish/fleshy to pale-pink round lesions, usually solid and more rarely cystic. The only peculiar feature of pancreatic NENs in MEN1 is the presence of multiple lesions, in contrast to sporadic pancreatic NENs that are usually solitary lesion (WHO 2019).

Microscopy

The histological hallmark of MEN1 is represented by the presence of multiple microtumors (Figure 24 A). They stain positive for neuroendocrine markers, such as synaptophysin and chromogranin-A, and show a low Ki-67 proliferation index (almost invariably <3%, G1). However, multiple microtumors may also occur in patients with VHL disease and, occasionally, in individuals without an apparent genetic syndrome. Regarding the histological architecture and cell composition, GEP-NENs encountered in MEN1 patients usually do not display peculiar morphological features that can be used in differentiating them with their sporadic counterparts. Along this line, within the pancreas, the main criterion is still represented by the presence of multiple lesions and microtumors, typically present in MEN1 patients, which can sometimes be associated with cystic aspects (Figure 24 B–C) (WHO Classification of Tumours Editorial Board 2019).

Treatment

The therapeutic approach of GEP-NENs occurring in MEN1 patients depends on numerous factors, such as the anatomic site and the size of the tumor, the multifocality, the expression of SSTRs, the stage and grade of the disease, the involvement of adjacent structures, the potential presence of distant metastases, and the patient comorbidities.

Dietary adjustments and medical treatments (e.g., anti-acids medications) can help in controlling major symptoms including hypoglycemia and hyperchlorhydria.

Of note, MEN1-associated GEP-NENs, and above all solitary and small lesions, may be amenable to surgical resection. A peculiarity is represented by gastrinomas, which can be very rarely surgically resected. Indeed, they are typically multiple and diffuse, displaced throughout the entire pancreas and

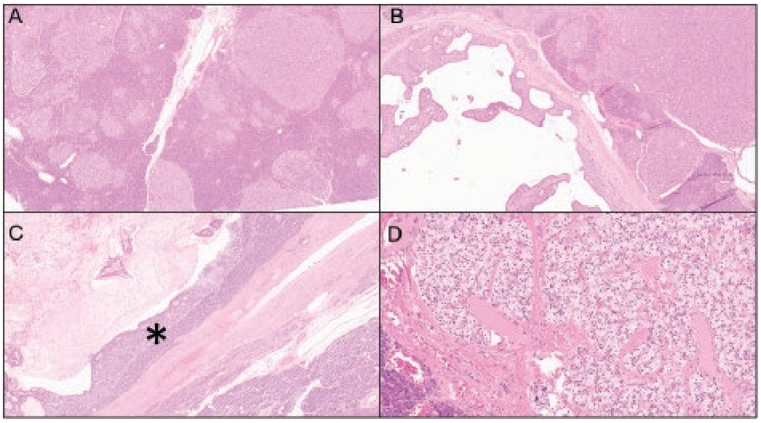

Figure 24 **A**. A classic example of microadenomatosis occurring in a pancreatic surgical specimen of a MEN1 patient (Hematoxylin-eosin staining, 2X magnification); **B**. The presence of microadenomatosis may be associated with cystic aspects (Hematoxylin-eosin staining, 4X magnification); **C**. Cystic appearance of a syndromic pancreatic neuroendocrine tumor [the asterisk indicates the neuroendocrine cell / cystic lining (Hematoxylin-eosin staining, 2X magnification)]; **D**. Classic clear cell appearance of a pancreatic neuroendocrine tumor arising in a VHL patient.

proximal duodenum. Thus, in such patients, surgical resection, which can be represented only by a total pancreatectomy, is not commonly recommended due to the extensive postoperative morbidity and also a similar long-term prognosis (Partelli et al. 2016). Of note, in the metastatic setting, it is important to highlight that liver metastases can be amenable of transarterial chemoembolization (TACE) (Fiore et al. 2014).

Targeted radionuclide therapy (radiolabeled somatostatin analogs such as 90Y-octreotide or 90Ylanreotide) is another option that can help in palliating symptoms in patients with widely metastatic disease refractory to other medical interventions (Kaemmerer et al. 2021). The recently developed immunotherapy with immune checkpoint inhibitors (e.g., anti-PD-1, anti-PD-L1 and anti-CTLA4) has not been already standardized in this context (Al-Toubah et al. 2020), and this consideration can be shared with the other syndromic GEP-NENs.

The Von Hippel-Lindau Syndrome (VHL)

Epidemiology, Molecular Biology, and Clinical Presentation

VHL is an autosomal dominant multisystem familial neoplasia syndrome that predisposes affected individuals to tumor development, with high penetrance and variable expression, and an incidence of around 1/36.000 individuals (Maher et al. 1991). Most patients have a demonstrable germline variation of the *VHL* gene, which is a tumor suppressor gene. It is located in the short arm of chromosome 3 (3p25–3p26) and encodes for the homonymous VHL protein (Seizinger et al. 1988).

Under normal tissue oxygen levels, the VHL protein forms a complex with other proteins, namely elongin B, elongin C, Cul2, and Rbx1, which in turn initiates ubiquitin mediated degradation of the hypoxia-inducible factors (HIFs) HIF-1a and HIF-2a. HIFs regulate the expression of several genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor receptor (EGFR), transforming growth factor-alpha (TGF-α), and glucose transporter-1 (GLUT1) genes. *VHL* mutations lead to the stabilization and activation of HIF-1a and HIF-2a, thus activating biological mechanisms with the overall effect of promoting angiogenesis, proliferation, and metabolism through the activation of VEGF, PDGF, EGFR, TGF-α, and GLUT1 (Singer et al. 2011).

The most common tumor types that can be encountered in VHL patients are hemangioblastomas (HBs) of the retina and central nervous system, clear cell renal cell carcinomas (ccRCC), pheochromocytoma (PCC), pancreatic serous cystadenomas and, for GEP-NENs, the classic neoplasm arising in the context of VHL is represented by pancreatic neuroendocrine tumors (Maher et al. 2011).

VHL is clinically diagnosed in patients with a family history and a HB of the retina or of central nervous system, or a PCC or a ccRCC. In patients without a family history, the diagnostic criteria are satisfied in the case of the presence of 2 or more HBs of the central nervous system, or of one HB of the central nervous system and a visceral tumor of the VHL spectrum (Latif et al. 1993). The most lethal lesions arising in VHL are represented by cerebellar tumor or ccRCC; the mean age of death due to complications related to this syndrome is <50 years old.

Specifically regarding GEP-NENs in VHL, it is of interest reporting that pancreatic neuroendocrine tumors are rarely the presenting tumor, but they can be diagnosed in up to 20% of patients (Hough et al. 1994). Pancreatic neuroendocrine tumors arising in VHL are usually slow growing and with a G1 grading; however, a malignant behavior is possible, and it is more often observed for those tumors greater than 3 cm in diameter at the time of diagnosis (Corcos et al. 2008). This kind of tumors are typically nonfunctioning, multiple, and located throughout the pancreatic gland (Jensen et al. 2008).

Imaging

As already stated for NENs in MEN1 patients, the sensitivity of CT, MRI, and US for identifying GEP-NENs is very high. Also for VHL-related NENs, the “molecular” techniques include somatostatin receptor imaging with 68Ga-DOTA-SSA PET/CT and high metabolism imaging with 18-FDG (DOPA) PET/CT.

The most used methodologies in the approach to VHL patients are CT and MRI. With MRI, pancreatic NENs usually show an intense and early enhancement in post-gadolinium images and frequently appear as hypervascular lesions with a typical arterial enhancement; although possible, cystic tumors are uncommon (Graziani et al. 2014; Libutti et al. 1998).

Macroscopy

Grossly, pancreatic NENs are represented by well-demarcated nodules, highly vascularized, variegated red–brown to yellow–tan, and usually oval or roundish. In contrast to pancreatic NENs arising in the context of MEN1, the background VHL-pancreas lacks nesidioblastosis-like aspects and/or hyperplasia of the islets of Langerhans (Pawlu et al. 2005).

As tumors grow, the vascularization of the central portions decreases and necrotic areas and calcifications may become more and more evident. Although not frequently, cystic PanNETs may also occur; although rarely seen, it should be clarified that cystic NENs in the pancreas are more commonly seen in tumors within VHL spectrum rather than in sporadic context.

Microscopy

The presence of a clear cell aspect (Figure 23 D) and of numerous small vessels is a histological hallmark of VHL-associated tumors. Such aspects are typically encountered in ccRCC and HB, and can also occur in pancreatic NENs. However, pancreatic NENs can also show a conventional morphology. In the context of VHL, tumor grading of pancreatic NENs is usually G1.

Treatment

Most patients present with no pancreatic-related symptoms; however, due to the potential metastatic behavior, surgical resection represents the treatment of choice for pancreatic NENs. In the syndromic scenario, other lesions should be excluded with imaging and a personalized treatment should be focused also taking into account the presence of other neoplasms (Delman et al. 2006).

Current recommendations for the treatment of pancreatic NENs in VHL patients are based on three key factors: 1) tumor size (≥3 cm), 2) presence of mutation in exon 3, and 3) a mass doubling time (≤ vs. >500 days). In cases of the presence of two or three of these criteria, there is the indication for surgical resection; in the case of one or no criteria, the patient should be carefully monitored by cross-sectional imaging (CT/MRI) every 6–12 months (one criterion) or 2–3 years (no criteria), respectively (Blansfield et al. 2007).

Liver is the most common site of metastases from pancreatic NENs. Metastatic liver disease can be treated by a combination of locoregional therapy (including ablation) and hepatic arterial chemotherapeutic infusion, as also specified for MEN1 patients.

Molecular targets for the medical treatment of neuroendocrine NENs in VHL patients have also been proposed, since the presence of a VHL-driven HIF deregulation may represent a potential target for precision oncology (Yao and Hoff 2007). Although some evidences have clarified this mechanism as possible target in VHL-associated ccRCC, further studies are needed to explore this possibility also for pancreatic NENs (Yao 2007).

The Neurofibromatosis Type 1 Syndrome (NF1)

Epidemiology, Molecular Biology, and Clinical Presentation

The neurofibromatoses are a heterogeneous group of autosomal-dominant inherited neurogenetic syndromes that include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. NF1 is the most common, occurring in 2500–3000 individuals per year worldwide (Huson et al. 1989). Nevertheless, approximately in 50% of cases, NF1 arises *de novo* in individuals with no known family history of such genetic syndrome (Friedman 1999).

NF1 results from germline mutations in the *NF1* gene that is located on chromosome 17 (Viskochil et al. 1990). This gene encodes for the neurofibromin, a ubiquitously expressed protein, which functions as a RAS-GTPase Activating Protein (RAS-GAP), overall resulting as a negative regulator of RAS activity. Consequently, such neurofibromin deficiency leads to an increased RAS signaling. NF1 can be therefore classified as a "RASopathy" (Tidyman and Rauen 2016).

Although the disease is usually fully penetrant by age 5, there is a high degree of variability in disease presentation and outcomes. The major defining features of NF1 include café-au-lait macules (CALMs), cutaneous neurofibromas, plexiform neurofibromas (PNF), axillary or inguinal freckling (increased number of freckles, small circular spots on the skin that are darker than the surrounding skin, because of deposits of melanin), optic pathway gliomas (OPG), Lisch nodules of iris (defined as pigmented hamartomatous nodular aggregates of dendritic melanocytes affecting the iris), and skeletal abnormalities (Upadhaya 2010).

Neurofibromas are benign peripheral nerve sheath tumors and are a major cause of morbidity in NF1 patients. Individuals with NF1 also exhibit an increased risk for leukemia, pheochromocytoma, breast carcinoma, glomus tumors, GEP-NENs, gastrointestinal stromal tumors (GISTs), melanomas, and rhabdomyosarcomas (Geschwind et al. 2018).

A clinical diagnosis of NF1 should be made if patients demonstrate at least two of the following: 1) Six or more CALMs/CALM-spots of at least 5 mm in size (before puberty) or 15 mm in size (after puberty); 2) freckling in the underarms (axillary) or inguinal region; 3) abnormal clumps of pigment on the colored portion of the eye (Lisch nodules); 4) certain abnormalities of bone development in the head (sphenoid wing dysplasia) or abnormal bowing of bones (pseudoarthrosis); 5) two or more neurofibromas of any type or one plexiform neurofibroma; 6) an affected parent/sibling with confirmed NF1.

Gastrointestinal system is involved in up to 25% of all NF1 patients; particularly, the upper intestinal tract is the most involved region and neurofibromas are the most common type of lesions, mostly located in the small intestines (Hirbe and Gutmann 2014).

Gastrointestinal tract neoplasms in NF-1 patients are more frequent than in the general population and occur in three main forms: i) hyperplasia of the submucosal and myenteric nerve plexuses and mucosal ganglioneuromatosis that leads to disordered gut motility; ii) GISTs with varying degrees of neural or smooth muscle differentiation; iii) distinctive somatostatin-rich carcinoid in the periampullary region of the duodenum. Clinical manifestations are variable and depend on the location and extent of mucosal involvement; symptomatic tumors are most commonly seen in the stomach and jejunum (Levy et al. 2005).

GEP-NENs occur in about 1% of patients with NF1 and may involve any part of the GI tract, but they display a special affinity for the duodenal and peri-ampullary region (Teixeira et al. 2016). Nonfunctioning somatostatin-producing tumors are the most common GEP-NENs detected in this setting, and usually involve the peri-ampullary region (Agaimy et al. 2012; Basile et al. 2010; Hamy et al. 2001; Levy et al. 2005; Pernet et al. 2010; Teixeira et al. 2016). They are usually small in size because of earlier recognition related to local obstructive symptoms. Therefore, the somatostatin syndrome, including diabetes mellitus, steatorrhea, and weight loss, is very rare in NF1 individuals. Symptoms are mode often the result of the mass effects, with jaundice and nonspecific abdominal pain.

Imaging

As already stated for other syndrome-related GEP-NENs, the sensitivity of CT, MRI, and US and of "molecular" imaging techniques for identifying NET is very high in NF1 patients as well. Specifically regarding periampullary neuroendocrine tumors, they tend to be avidly enhancing polypoid, intraluminal, or intramural masses on CT and MRI (Levy et al. 2005).

Macroscopy

Grossly, NENs arising in the context of NF1 syndrome are indistinguishable from their sporadic counterparts. In the case of macroscopic analysis of a pancreaticoduodenectomy, in addition to the classic neuroendocrine lesion in the ampullary/periampullary region, some duodenal GISTs and neurofibromas can be detected. On the cut surface, the neuroendocrine lesion is usually jarring due to the presence of calcifications.

Microscopy

Usually, all GEP-NENs arising in NF1 are represented by G1 lesions, with a Ki-67 proliferation index <3% also in those rare metastasizing lesions. Most neuroendocrine tumors developing in the context of NF1, as already described, arise in the ampullary and peri-ampullary region, and show "glandular" structures containing psammoma bodies. The high incidence of psammoma bodies (psammomatous calcifications) in the ampullary lesions of patients with NF1 can be of help in establishing the histological diagnosis (Partelli et al. 2016; Pernet et al. 2010). Sporadic somatostatinomas arising in the pancreas usually do not show this distinctive feature. Immunohistochemically, they consistently express somatostatin and synaptophysin, but chromogranin-A is usually weak or more focal. Metastases have been described in up to 27% of somatostatin-producing tumors in NF1 patients, and mainly to regional lymph nodes. They appear to be less aggressive than their sporadic counterparts (Hamy et al. 2001). Of note, a tumor diameter of more than 2 cm and the infiltration of the outer-smooth muscle layer increase the risk of nodal and distant metastases (Coltin et al. 2022).

Treatment

As for genetic syndromes in general, a regular monitoring is essential for managing the disease. For NF1, annual physical exams are recommended for all patients, in addition to blood pressure screening and frequent eye-exams. Children should undergo annual ophthalmologic exams, as well as regular developmental assessments. Advanced imaging techniques (MRI, PET, or PET/CT) are used for the follow-up of internal tumors, depending on location(s) and symptoms. As for other GEP-NENs, endoscopic excision can be considered in cases of tumors with a diameter < than 1 cm, whereas neoplasms larger than 1 cm usually require surgical resection. Since the most common location of GEP-NENs in NF1 patients is represented by ampullary/periampullary lesions, the most common surgical intervention is represented by pancreaticoduodenectomy (Whipple's procedure) (Tanaka et al. 2000). NF1 patients may undergo surgery also to remove particularly troublesome or disfiguring tumors, depending on their size and location, and different orthopedic devices may help to improve the mobility in some cases. The first specific medical treatment for NF1 patients was approved by the US Food and Drug Administration (FDA) in April 2020 to treat pediatric patients. It is represented by selumetinib, a kinase inhibitor that is used for blocking the growth of neurofibromas (Coltin et al. 2022).

References

Agaimy, A., Vassos, N., and Croner, R.S. (2012). Gastrointestinal manifestations of neurofibromatosis type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. *Int J Clin Exp Pathol* 5: 852–862.

Agarwal, S.K. (2013). Multiple endocrine neoplasia type 1. *Front Horm Res* 41: 1–15.

Al-Toubah, T., Cives, M., and Strosberg, J. (2020). Novel immunotherapy strategies for treatment of neuroendocrine neoplasms. *Transl Gastroenterol Hepatol* 5: 54.

Basile, U., Cavallaro, G., Polistena, A. et al. (2010). Gastrointestinal and retroperitoneal manifestations of type 1 neurofibromatosis. *J Gastrointest Surg* 14 (1): 186–194.

Blansfield, J.A., Choyke, L., Morita, S.Y. et al. (2007). Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). *Surgery* 142 (6): 814–818; discussion 818.e1-2.

Brandi, M.L., Gagel, R.F., Angeli, A. et al. (2001). Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 86 (12): 5658–5671.

Casey, R.T., Saunders, D., Challis, B.G. et al. (2017). Radiological surveillance in multiple endocrine neoplasia type 1: a double-edged sword? *Endocr Connect* 6 (3): 151–158.

Coltin, H., Perreault, S., Larouche, V. et al. (2022). Selumetinib for symptomatic, inoperable plexiform neurofibromas in children with neurofibromatosis type 1: a national real-world case series. *Pediatr Blood Cancer* 69 (8): e29633.

Corcos, O., Couvelard, A., Giraud, S. et al. (2008). Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. *Pancreas* 37 (1): 85–93.

Crona, J. and Skogseid, B. (2016). GEP-NETS UPDATE: genetics of neuroendocrine tumors. *Eur J Endocrinol* 174 (6): R275–90.

Delman, K.A., Shapiro, S.E., Jonasch, E.W. et al. (2006). Abdominal visceral lesions in von Hippel-Lindau disease: incidence and clinical behavior of pancreatic and adrenal lesions at a single center. *World J Surg* 30 (5): 665–669.

Fiore, F., Del Prete, M., Franco, R. et al. (2014). Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. *Endocrine* 47: 177–182.

Francis, J.M., Kiezun, A., Ramos, A.H. et al. (2013). Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. *Nat Genet* 45 (12): 1483–1486.

Friedman, J.M. (1999). Epidemiology of neurofibromatosis type 1. *Am J Med Genet* 89: 1–6.

Fujii, T., Kawai, T., Saito, K. et al. (1999). MEN1 gene mutations in sporadic neuroendocrine tumors of foregut derivation. *Pathol Int* 49 (11): 968–973.

Geschwind, D.H., Paulson, H.L., and Klein, C. (2018). *Handbook of Clinical Neurology*, vol. 148 (3rd series) Neurogenetics, Part II. Amsterdam: Elsevier.

Graziani, R., Mautone, S., Vigo, M. et al. (2014). Spectrum of magnetic resonance imaging findings in pancreatic and other abdominal manifestations of Von Hippel–Lindau disease in a series of 23 patients: a pictorial review. *Jop* 15: 1–18.

Hamy, A., Heymann, M.F., Bodic, J. et al. (2001). Duodenal somatostatinoma. Anatomic/clinical study of 12 operated cases. *Ann Chir* 126: 221–226.

Hirbe, A.C. and Gutmann, D.H. (2014). Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol* 13: 834–843.

Hough, D.M., Stephens, D.H., Johnson, C.D., and Binkovitz, L.A. (1994). Pancreatic lesions in von Hippel-Lindau disease: prevalence, clinical significance, and CT findings. *Am J Roentgenol* 162: 1091–1094.

Huson, S.M., Compston, D.A., and Harper, P.S. (1989). A genetic study of von Recklinghausen neurofibromatosis in South East Wales. II. Guidelines for genetic counselling. *J Med Genet* 26: 712–721.

Jensen, R.T., Berna, M.J., Bingham, D.B., and Norton, J.A. (2008). Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 113 (7 Suppl): 1807–1843.

Kaemmerer, D., Twrznik, M., Kulkarni, H.R. et al. (2021). Prior resection of the primary tumor prolongs survival after peptide receptor radionuclide therapy of advanced neuroendocrine neoplasms. *Ann Surg* 274: 45–53.

Kann, P.H., Balakina, E., Ivan, D. et al. (2006). Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. *Endocr Relat Cancer* 13 (4): 1195–1202.

Kornaczewski Jackson, E.R., Pointon, O.P., Bohmer, R., and Burgess, J.R. (2017). Utility of FDGPET imaging for risk stratification of pancreatic neuroendocrine tumors in MEN1. *J Clin Endocrinol Metab* 102: 1926–1933.

Latif, F., Tory, K., Gnarra, J. et al. (1993). Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 260 (5112): 1317–1320.

Levy, A.D., Patel, N., Dow, N. et al. (2005). Abdominal neoplasms in patients with neurofibromatosis type 1: radiologic-pathologic correlation. *Radiographics* 25: 455–480.

Libutti, S.K., Choyke, P.L., Bartlett, D.L. et al. (1998). Pancreatic neuroendocrine tumors associated with von Hippel Lindau disease: diagnostic and management recommendations. *Surgery* 124 (6): 1153–1159.

Maher, E.R., Iselius, L., Yates, J.R. et al. (1991). von Hippel-Lindau disease: a genetic study. *J Med Genet* 28: 443–447.

Maher, E.R., Neumann, H.P., and von Richard, S. (2011). Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet* 19: 617–623.

Partelli, S., Cirocchi, R., Crippa, S. et al. (2016). Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *Br J Surg* 104: 34–41.

Pawlu, C., Bausch, B., Reisch, N., and Neumann, H.P.H. (2005). Genetic testing for pheochromocytoma-associated syndromes. *Ann Endocrinol* 66: 178–185.

Pellegata, N.S., Quintanilla-Martinez, L., Siggelkow, H. et al. (2006). Germline mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Pnas* 103: 15558–15563.

Pernet, C., Kluger, N., Du-Thanh, A. et al. (2010). Somatostatin-producing endocrine tumour of the duodenum associated with type 1 neurofibromatosis. *Acta Derm Venereol* 90: 320–321.

Seizinger, B.R., Rouleau, G.A., Ozelius, L.J. et al. (1988). Von Hippel-Lindau disease maps to the region of chromosome 3 associated with renal cell carcinoma. *Nature* 332 (6161): 268–269.

Singer, E.A., Bratslavsky, G., Middelton, L. et al. (2011). Impact of genetics on the diagnosis and treatment of renal cancer. *Curr Urol Rep* 12 (1): 47–55.

Sundin, A., Arnold, R., Baudin, E. et al. (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology* 105 (3): 212–244.

Tanaka, S., Yamasaki, S., Matsushita, H. et al. (2000). Duodenal somatostatinoma: a case report and review of 31 cases with special reference to the relationship between tumor size and metastasis. *Pathol Int* 50 (2): 146–152.

Teixeira, F., Menegozzo, C.A.M., Sdd, C.N. et al. (2016). Pancreaticoduodenectomy in patients with type 1 Neurofibromatosis: report of two cases and literature review. *Int J Surg Case Rep* 27: 36–40.

Thakker, R.V. (2014). Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). *Mol Cell Endocrinol* 386 (1–2): 2–15.

Tidyman, W.E. and Rauen, K.A. (2016). Pathogenetics of the RASopathies. *Hum Mol Genet* 25: 123–132.

Turner, J.J., Christie, P.T., Pearce, S.H. et al. (2010). Diagnostic challenges due to phenocopies: lessons from Multiple Endocrine Neoplasia type1 (MEN1). *Hum Mutat* 31 (1): E1089–101.

Upadhyaya, M. (2010). Neurofibromatosis type 1: diagnosis and recent advances. *Expert Opin Med Diagn* 4: 307–322.

van Asselt, S.J., Brouwers, A.H., van Dullemen, H.M. et al. (2015). EUS is superior for detection of pancreatic lesions compared with standard imaging in patients with multiple endocrine neoplasia type 1. *Gastrointest Endosc* 81 (1): 159–167.

Viskochil, D., Buchberg, A.M., Xu, G. et al. (1990). Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* 62 (1): 187–192.

WHO Classification of Tumours Editorial Board. (2019). *Digestive System Tumours*, 5e. Lyon: International Agency for Research on Cancer (IARC).

Yao, J.C. (2007). Neuroendocrine tumors. Molecular targeted therapy for carcinoid and islet-cell carcinoma. *Best Pract Res Clin Endocrinol Metab* 21: 163–172.

Yao, J.C. and Hoff, P.M. (2007). Molecular targeted therapy for neuroendocrine tumors. *Hematol Oncol Clin North Am* 21: 575–581.

Key Take Home Messages

Neuroendocrine neoplasms of the gastrointestinal tract include a large spectrum of entities with numerous differences related to localization, morphology and differentiation, genetics and molecular profile, which all affect diagnostic procedures, prognosis, and therapy. Most relevant factors for prognosis remain the tumor stage and grade; entity-specific prognostic and predictive markers have been discussed in detail in the previous sections and mostly need further validation through prospective trials.

Clinical Management

- An accurate classification and risk assessment based on clinical and biochemical features, imaging, morphology and, where indicated, molecular pathology is mandatory for optimal patients' management. Genetic testing should be carried out in patients with multiple NENs, positive family history, and in young patients with gastrinoma.
- Surgery is the treatment of choice for NETs G1-G2 in local/locoregional disease as well as in locally advanced NETs of the small intestine due to the risk of obstruction. Different approaches (e.g., minimal invasive vs. radical) depend on tumor localization. Medical treatment of symptomatic tumors is required prior to intervention.
- The treatment of choice for advanced and/or metastatic tumors depends on numerous factors and includes locoregional ablative therapies, chemotherapy, peptide radioreceptor therapy (PPRT), somatostatin analogue-based therapy, and therapy with mTOR and multikinase inhibitors and interferon-alpha. For details and updates, please see clinical guidelines listed below.

Areas for Further Research

- Development of progression models based on deep genetic and epigenetic profiling of NENs in order to understand the natural history of these lesions, to uncover possible unknown relationships between NETs, NECs, and MiNENs of a given organ and, eventually, to identify biomarkers for prediction of disease progression and prognosis.
- High-resolution "omics" approaches in order to disclose tumor heterogeneity and to identify predictors of therapy response and therapy resistance for tailored treatment approaches.
- Development of highly sensitive and specific tracers and ligands for theranostics.
- Identification of new personalized therapeutic approaches for advanced disease by addressing NEN's genome, microenvironment, and key oncological checkpoints.

Trusted Websites for Further Reading

https://www.enets.org/guidelines.html

https://www.esmo.org/guidelines/guidelines-by-topic/endocrine-and-neuroendocrine-cancers

https://nanets.net/net-guidelines-library

25 Epidemiology, Pathology, Diagnosis, Prevention, and Management of Unknown Primary Cancer

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Definition; Cancer of Unknown Primary (CUP) is a term used to describe when multiple metastatic tumors arise in the absence of an obviously identifiable primary cancer. However, trying to ascertain the source is important as it impacts on the optimal treatment and outcomes. CUPs should be distinguished from lymphomas, melanomas, and sarcomas, that may commonly arise in multiple sites but have different management guidelines and they are not treated under the scope of CUPs.

Epidemiology

CUPs are uncommon and cause less than 2–4% of all cancers globally. It is likely this figure will also decrease further as iterative improvements occur in the pathological, molecular pathological and radiological diagnosis locate the primary tissue source or at least the approximate histological stem cell type of origin. In the west CUP accounts for more cases in women than men. This is especially true for those aged 75 and above.

Mortality rates are especially high in those over 90 years of age as well as women living in deprived neighborhoods.

Most CUPs have the presumed histological diagnosis made but in over 50% of cases the primary lesion is never identified.

Risk Factors and Prevention

The major risk factors for CUPs can be broadly ascribed to the histological classification; however, the main etiological factors with exemplars are listed (Table 1).

For squamous cell cancers of the aerodigestive tract, it is overwhelmingly related to cigarette smoking and alcohol consumption. Whereas for adenocarcinomas of the stomach, colon, and kidney, it is overwhelmingly diet and body weight. In anal and cervical squamous cancers human papilloma virus is the main cause.

For many CUPs inherited genetics also plays a role including prostate, ovarian, pancreas, thyroid, and skin.

The best forms of prevention include lifestyle modifications. This especially complete cessation of cigarette smoking including passive smoke. In addition, moderation of alcohol consumption to very low levels < 5 units per week. Furthermore, avoidance of high sugar, saturated fat, transfat, and restricted diets consisting of junk food. Moreover, avoidance of high-risk activities including unprotected sex, sun exposure, and sedentary lifestyle.

There are several screening programs for certain diseases including sites of known CUPs the paradigms being colorectal, ovarian, and prostate. Ensuring the population attend these appointments, at the current age cohorts, is vital. This is becoming steadily more acceptable, thereby improving compliance, since some of the programmes involve simple blood tests which is more likely to pick up CUPs like serum PSA and the PSA kinetic rise on subsequent retesting.

Diagnosis and Pathology

Patients with CUP most commonly present symptomatically and are more likely to present as an acute admission than patients with a known tumor type. In England 56% of CUP patients present as an initial emergency presentation (National Cancer Intelligence Network 2014). Patients presenting through these routes are often symptomatic, with borderline or poor performance status, which may in turn influence the overall outcome.

The diagnostic work up of CUP patients should include a full clinical history – focusing on symptomatology and risk factors. This should be accompanied with a detailed and thorough examination of the body including lymph nodes, skin, including remote skin regions (hairline and soles of feet), retina, breast and vaginal examination in women, and testicular examination in men.

Gastrointestinal Oncology: A Critical Multidisciplinary Team Approach, Second Edition. Edited by Janusz A. Z. Jankowski.
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Table 1 For cancer prevention plan for CUP.

I. Cancer risk in population	35–50% (geographical variation)	
II. Cancer cases which can be prevented	33–40%	Prevention strategies Smoking replacement tools Population education Product taxation Medical intervention
Cancer etiological factor		Types of cancer that are preventable
Cigarette smoke	~15% cancer risk	
Passive smoking	~2%	
Active smoking	~16%	
Weight;	~6% cancer risk	Low/moderate
Overweight/obesity/morbid obesity	*~2%/6%/10% respectively*	
UV Radiation	~5% cancer risk	Moderate/high
Occupational;	~5% cancer risk	High
Particulate and chemical fumes		
Infections;	~5%	99% cervical and 90% anal cancers are preventable
HPV		
Hepatitis		
Alcohol	~5%	Moderate/high
Diet;	~4%	50% colorectal cancers are preventable
Salt, sugar, and transfats		
III. Cancer/Precancer cases which cannot be prevented	30%	Types of cancers that can't be prevented
Cancer etiological factor		
Inherited genetics	~15%	Colorectal 40% not preventable, Breast 75% not preventable unless prophylactic mammectomy
Elderly > 80 years	~5–10%	Prostate cancer 99% not preventable
Idiopathic childhood	~1–2%	Childhood cancers 99% not preventable
Global environmental pollution	~2–3%	NH lymphoma 97% not preventable
IV. Cancer cases with unknown etiology or complex etiology	30%	Testicular 99% not preventable Young persons' cancers 99% not preventable

Men have a ~5–7% increased benefit from cancer prevention enaction strategies compared with women adapted from Brown KF, Rumgay H and Dunlop C et al. The fraction of cancer attributable to known risk factors in England. Brit J Cancer 2018;118:1130–1141.

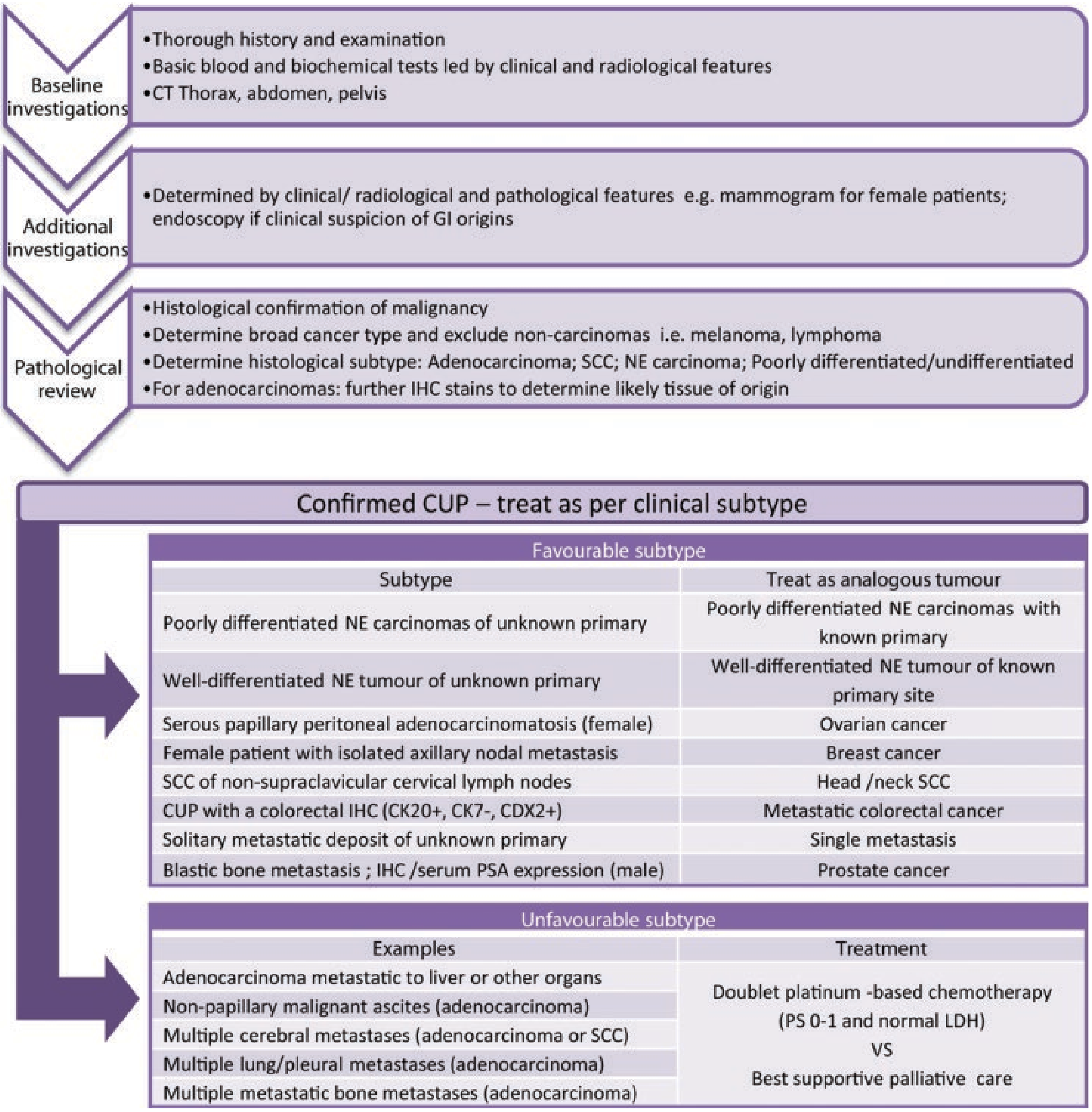
Where a cancer diagnosis is suspected a CT thorax, abdomen and pelvis with contrast should be undertaken. The focus of further diagnostics is to determine the potential primary tumor disease type and identify highly treatable and potentially curable cancer types. Further diagnostic imaging should be guided by the clinical history and examination depending on the signs, symptoms, and suspected potential primary tumor diagnosis (Figure 1).

The diagnostic work-up and specialized tests for finding potential primary diagnosis include mammography or MR breast for female patients presenting with axillary lymphadenopathy; GI endoscopy for suspected GI primary tumor in patients with upper gastrointestinal symptoms or pathology in keeping with a GI primary; colonoscopy in patients with lower GI symptoms or pathology in keeping with lower GI primary.

Serum tumor biomarkers, such as CEA (colon), CA19-9 (hepatobiliary/pancreas), Ca125 (ovary/primary peritoneal), PSA (prostate), HCG (germ cell tumors), AFP (germ cell tumors and hepatoma), Chromogranin-A (NETs), and GI hormone profile (NETs) should be applied where appropriate. These biomarkers however vary in their specificity and sensitivity so should be interpreted within the clinical context of the patient taking into account radiological and pathological findings. Serum tumor biomarkers are not diagnostic and in CUP it is common to see elevation of multiple serum tumor biomarkers (Figure 2).

PET CT is used in specific scenarios in CUP and its introduction as a standard of care diagnostic is currently being investigated. At present PET CT is indicated in patients with solitary metastases where potential radical treatment is being considered, patients presented with limited nodal disease for example where a head and neck SCC is suspected, and bone only metastases which may be of benefit when determining a site for biopsy.

Where no primary diagnosis is found after specialist review within a CUP MDT, the diagnosis of CUP is confirmed. Further subtyping into a "favourable" or "unfavourable" subset can be undertaken depending on clinical, pathological, and radiological findings. For 20% of cases within the "favourable" subtype, clinical features can align the patient to a potential primary tumor type and these patients should be managed as per that tumor type (for examples see Figure 1). Patients within the



Baseline investigations

- Thorough history and examination
- Basic blood and biochemical tests led by clinical and radiological features
- CT Thorax, abdomen, pelvis

Additional investigations

- Determined by clinical/ radiological and pathological features e.g. mammogram for female patients; endoscopy if clinical suspicion of GI origins

Pathological review

- Histological confirmation of malignancy
- Determine broad cancer type and exclude non-carcinomas i.e. melanoma, lymphoma
- Determine histological subtype: Adenocarcinoma; SCC; NE carcinoma; Poorly differentiated/undifferentiated
- For adenocarcinomas: further IHC stains to determine likely tissue of origin

Confirmed CUP – treat as per clinical subtype

Favourable subtype

Subtype	Treat as analogous tumour
Poorly differentiated NE carcinomas of unknown primary	Poorly differentiated NE carcinomas with known primary
Well-differentiated NE tumour of unknown primary	Well-differentiated NE tumour of known primary site
Serous papillary peritoneal adenocarcinomatosis (female)	Ovarian cancer
Female patient with isolated axillary nodal metastasis	Breast cancer
SCC of non-supraclavicular cervical lymph nodes	Head /neck SCC
CUP with a colorectal IHC (CK20+, CK7-, CDX2+)	Metastatic colorectal cancer
Solitary metastatic deposit of unknown primary	Single metastasis
Blastic bone metastasis ; IHC /serum PSA expression (male)	Prostate cancer

Unfavourable subtype

Examples	Treatment
Adenocarcinoma metastatic to liver or other organs	Doublet platinum -based chemotherapy (PS 0-1 and normal LDH) VS Best supportive palliative care
Non-papillary malignant ascites (adenocarcinoma)	
Multiple cerebral metastases (adenocarcinoma or SCC)	
Multiple lung/pleural metastases (adenocarcinoma)	
Multiple metastatic bone metastases (adenocarcinoma)	

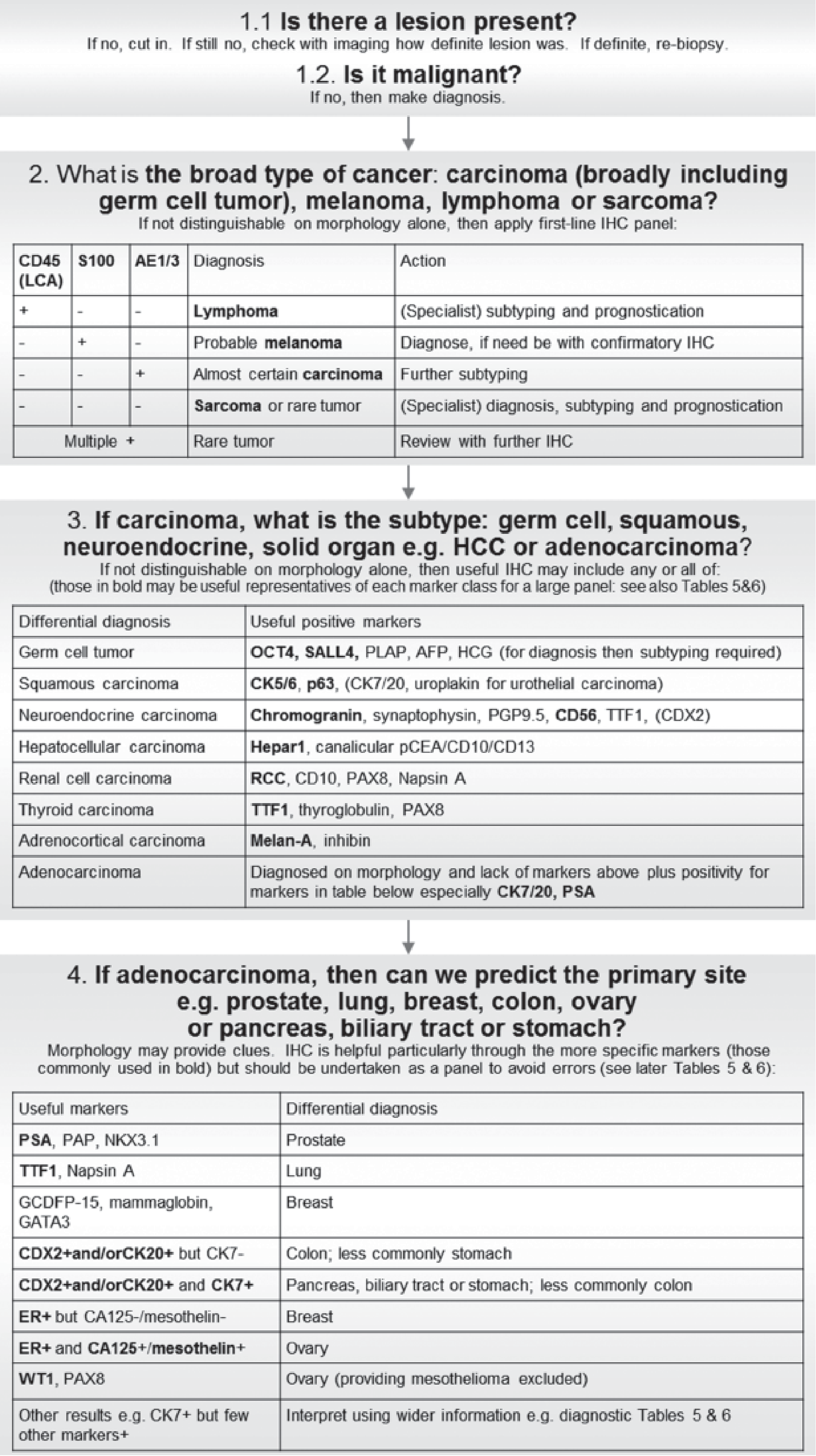
Figure 1 Investigation Plan for CUP (Conway, A.-M et al. 2018 / Springer Nature / Public Domain CC BY 4.0).

"unfavourable" CUP subtype (~80%) should be considered for generic SACT (systemic anticancer therapy) for CUP if they are well enough or be considered for clinical trials if available. If patients are of a poor performance status and not fit for SACT then they should receive best supportive care with optimization of symptom control.

Tissue Diagnosis and IHC

CUP is a diagnosis of exclusion and meticulous review of pathology is pivotal to determining a diagnosis and identifying treatable and potentially curable tumors (e.g. lymphoma and germ cell tumors). The initial step is the confirmation of malignancy and then exclusion of melanoma, lymphoma, or sarcoma. Once these have been excluded, carcinomas can be subtyped into squamous, neuroendocrine, solid organ (including liver, renal, thyroid, and adrenal), and adenocarcinoma. The final step for metastatic carcinoma diagnosis is the determination of the likely primary tumor site, e.g., in adenocarcinoma these may include lung, breast, pancreas, stomach, colon, ovary, kidney, and prostate; this can be achieved with the use of tissue-specific IHC markers.

The most common histological subtypes of CUP are adenocarcinomas (60%), squamous (5%), and neuroendocrine (5%) cancers, with the remaining 30% comprising of poorly/undifferentiated carcinomas. For adenocarcinoma, additional



1.1 **Is there a lesion present?**

If no, cut in. If still no, check with imaging how definite lesion was. If definite, re-biopsy.

1.2. **Is it malignant?**

If no, then make diagnosis.

2. What is **the broad type of cancer: carcinoma (broadly including germ cell tumor), melanoma, lymphoma or sarcoma?**

If not distinguishable on morphology alone, then apply first-line IHC panel:

CD45 (LCA)	**S100**	**AE1/3**	Diagnosis	Action
+	-	-	**Lymphoma**	(Specialist) subtyping and prognostication
-	+	-	Probable **melanoma**	Diagnose, if need be with confirmatory IHC
-	-	+	Almost certain **carcinoma**	Further subtyping
-	-	-	**Sarcoma** or rare tumor	(Specialist) diagnosis, subtyping and prognostication
Multiple +			Rare tumor	Review with further IHC

3. **If carcinoma, what is the subtype: germ cell, squamous, neuroendocrine, solid organ e.g. HCC or adenocarcinoma?**

If not distinguishable on morphology alone, then useful IHC may include any or all of:
(those in bold may be useful representatives of each marker class for a large panel: see also Tables 5&6)

Differential diagnosis	Useful positive markers
Germ cell tumor	**OCT4**, **SALL4**, PLAP, AFP, HCG (for diagnosis then subtyping required)
Squamous carcinoma	**CK5/6**, **p63**, (CK7/20, uroplakin for urothelial carcinoma)
Neuroendocrine carcinoma	**Chromogranin**, synaptophysin, PGP9.5, **CD56**, TTF1, (CDX2)
Hepatocellular carcinoma	**Hepar1**, canalicular pCEA/CD10/CD13
Renal cell carcinoma	**RCC**, CD10, PAX8, Napsin A
Thyroid carcinoma	**TTF1**, thyroglobulin, PAX8
Adrenocortical carcinoma	**Melan-A**, inhibin
Adenocarcinoma	Diagnosed on morphology and lack of markers above plus positivity for markers in table below especially **CK7/20, PSA**

4. **If adenocarcinoma, then can we predict the primary site e.g. prostate, lung, breast, colon, ovary or pancreas, biliary tract or stomach?**

Morphology may provide clues. IHC is helpful particularly through the more specific markers (those commonly used in bold) but should be undertaken as a panel to avoid errors (see later Tables 5 & 6):

Useful markers	Differential diagnosis
PSA, PAP, NKX3.1	Prostate
TTF1, Napsin A	Lung
GCDFP-15, mammaglobin, GATA3	Breast
CDX2+and/orCK20+ but CK7-	Colon; less commonly stomach
CDX2+and/orCK20+ and **CK7+**	Pancreas, biliary tract or stomach; less commonly colon
ER+ but CA125-/mesothelin-	Breast
ER+ and **CA125**+/**mesothelin**+	Ovary
WT1, PAX8	Ovary (providing mesothelioma excluded)
Other results e.g. CK7+ but few other markers+	Interpret using wider information e.g. diagnostic Tables 5 & 6

Figure 2 Immunohistochemistry markers for determining tissue of origin of CUP (adapted from ESMO guidelines).
CK, cytokeratin; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor 1; ER, estrogen receptor; PR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein 15; WT-1, Wilms tumor gene 1; PSA, prostate-specific antigen.
From Standards and datasets for reporting cancers Authors: Professor John B Schofield, Maidstone and Tunbridge Wells NHS Trust Dr Karin Oien, Institute of Cancer Sciences, University of Glasgow **Dataset for histopathological reporting of cancer of unknown primary (CUP) and malignancy of unknown primary origin (MUO)** RCP **July 2018** https://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html

appropriate IHC markers may determine the tumor origins. Firstly, primary IHC markers, cytokeratin-7 and 20 (CK7/CK20), should be applied, followed by tissue-specific markers; for example, TTF1, ER and PR, and PSA can identify lung, breast and gynecological, and prostate cancers, respectively (2) (ESMO guidelines) (see Figure 2). In addition, the Royal College of Pathologists have developed guidance 2018 with a pathological approach to CUP based on previous ESMO guidelines (Figure 2).

Identification of primary tumor diagnosis is an important step in management of patients presenting as CUP; however, multiple investigations and IHC stains may delay patients starting definitive treatment. In addition to the specific subtypes there are two further commonly misclassified tumor types that lack positive IHC markers but are now recognized disease-specific subtypes that can be identified via diagnostic algorithms within CUP. These include intrahepatic cholangiocarcinoma (liver only metastases or dominant liver lesion), TTF1 negative NSCLC, TTF1 positive NSCLC, renal cell carcinoma, serous carcinoma, salivary gland carcinoma, and breast carcinoma. Recent evidence has highlighted these as commonly presenting as CUP and new guidelines for diagnosis have been recommended and likely to be incorporated into updated ESMO guidance emphasizing the importance of careful radiological and pathological review from the CUPISCO study (Chantal et al. 2021).

Molecular Testing to Reveal Tissue-of-origin

There has been extensive research into molecular profiling for tissue-of-origin predictions in CUP including using gene expression assays and more recently DNA methylation. Retrospective nonrandomized studies have suggested that treating patients based on molecular profiling predictions improves survival (Hainsworth et al. 2013; Moran et al. 2016); however, more recent prospective randomized trials have not shown positive survival outcomes with this approach (Fizazi et al. 2019; Hayashi et al. 2019). Therefore, no current international guidelines support molecular tissue-of-origin predictions for the identification of potential primary tumor site.

Molecular Profiling for Predictive Biomarkers

Whole genome sequencing and targeted mutation panel sequencing (NGS – next generation sequencing) are increasingly performed in known tumor types to stratify patients to targeted therapies and immunotherapy. Although increasingly performed at present there is a lack of sufficient clinical evidence to support this approach to guide therapy as standard care. It is hoped the CUPISCO study (NCT03498521), which has now completed recruitment, will provide this evidence to support genomic-driven treatment stratification in CUP. Where funded or accessible through clinical trials both targeted and/or whole genome sequencing may find potential targets for therapies currently licensed in other tumor types or direct clinical trial recruitment. There are currently three tumor agnostic biomarkers that predict response to either targeted or immunotherapies and can be assessed for in CUP. NTRK fusions are predictive of response to NTRK inhibitors and MSI high/dMMR or high tumor mutation burden indicates potential benefit of immunotherapy. Access to therapy indicated by these biomarkers at present relies on clinical trials or compassionate access schemes; apart from NTRK inhibitors.

Medical Imaging in the form of CT scans, MRI, PET, and scintigraphy are usually employed to ascertain structural lesions in solid organs. One particular exemplar of the latter is octreotide scans using radioactive indium 111-label for NETs. Whereas endoscopy will be used to identify and biopsy lesions in the upper and lower digestive tract as well as aerodigestive tract and urogenital tract.

Biopsy under radiological guidance is also key to obtain samples for pathological examination. However, sometimes bone marrow aspiration and bone marrow biopsy are also done to obtain tumor cells caught in the marrow.

Where fluid has collected in internal spaces thoracocentesis, and paracentesis will be undertaken.

Prognosis and Management

All CUPs are TNM stage II and above by definition as they have spread from the original organ. Most will already be stage IV as they are fully disseminated by time of diagnosis. In general the more localized, and the better differentiated and the better the prognosis.

Cancer of unknown primary (CUP) is a heterogeneous group of metastatic cancers for which a standardized diagnostic work-up fails to identify the site of origin (Figure 3). CUPs are characterized by early metastatic dissemination, an undifferentiated phenotype, an aggressive clinical course, poor response to empiric chemotherapy and, consequently, a short life expectancy. The average survival for all CUPs is less than 1 year but the variation is very wide as some lesions are more sensitive to initial therapy.

Surgery

In CUP management, surgery has a limited role in initial resection for histological diagnosis, debulking of localized large lesions, and palliative procedures.

Radiotherapy

Definitive radiotherapy is an option for patients with localized disease.

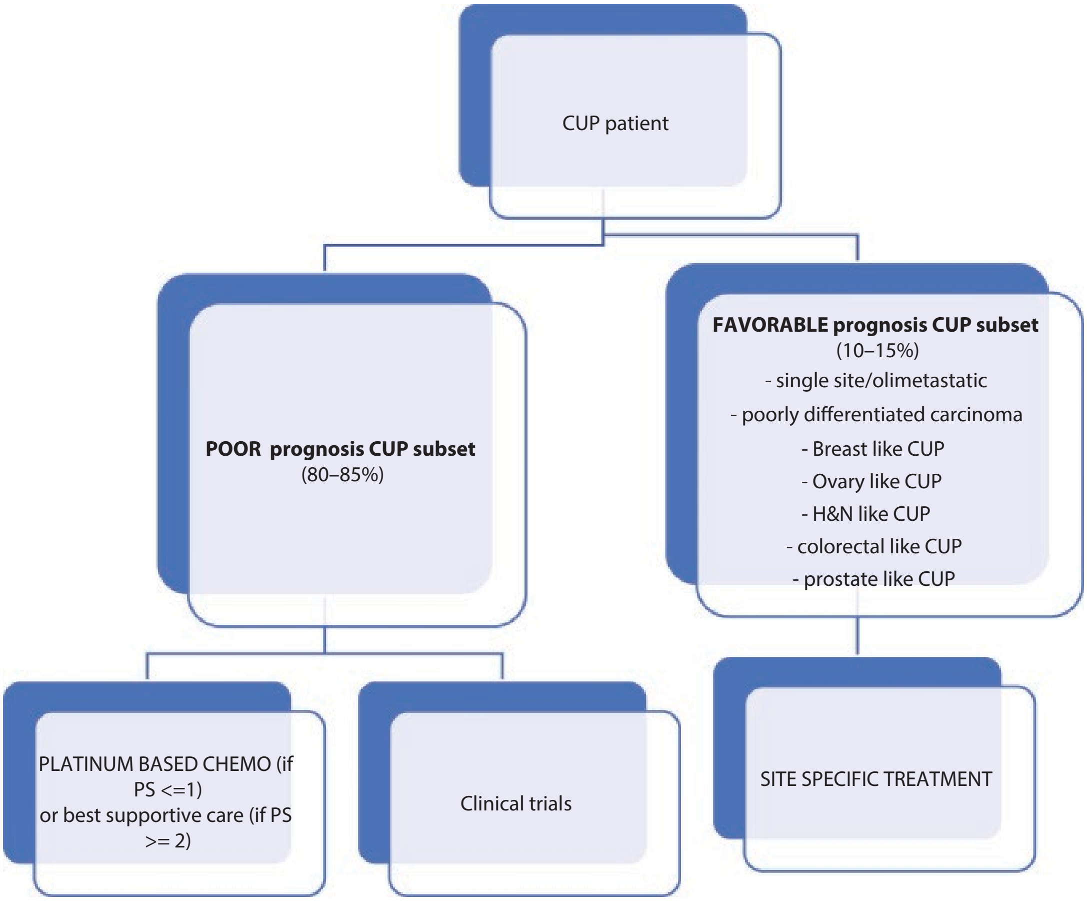

CUP patient
POOR prognosis CUP subset
(80–85%)
FAVORABLE prognosis CUP subset
(10–15%)
- single site/olimetastatic
- poorly differentiated carcinoma
- Breast like CUP
- Ovary like CUP
- H&N like CUP
- colorectal like CUP
- prostate like CUP
PLATINUM BASED CHEMO (if PS <=1)
or best supportive care (if PS >= 2)
Clinical trials
SITE SPECIFIC TREATMENT

Figure 3 CUP management algorithm.

Adjuvant radiotherapy could be considered after lymph node dissection for limited disease or inadequate nodal dissection with multiple positive lymph nodes.

Palliative radiotherapy plays an essential role for symptomatic patients.

Brachytherapy is used in areas where external beam radiotherapy might lead to wider field side effects, especially the breast.

Chemotherapy

Therapy should be individually tailored according to the clinicopathological subset to which the patient belongs.

The so-called “good prognosis” CUP patients, accounting for about 15–20% total CUP diagnoses (i.e. CUPs of possible breast, head, and neck squamous-cell, germ-cell, or neuroendocrine origin), should be treated similarly to patients with equivalent metastatic known primary tumors.

Patients with “poor-risk CUP” instead have a poor prognosis and are generally treated with empiric chemotherapy with poor clinical results (response rates of around 20% and median overall survival of 6–12 months).

No preferred regimen have emerged so far.

Usually for fit patients with a performance status < or = 1 and normal lactate dehydrogenase (LDH) it’s suggested a platinum-based doublet chemotherapy. For fragile patients instead with a performance status > or = 2 it could be considered a monochemotherapy or the best supportive care.

For adenocarcinoma and poorly differentiated lesions several tested regimens are available including

- Carboplatin plus paclitaxel (Taxol®), with or without etoposide (VP-16)
- Carboplatin plus docetaxel (Taxotere®)
- Cisplatin and/or gemcitabine and/or docetaxel
- Irinotecan (Camptosar®) and/or carboplatin and/or gemcitabine
- Oxaliplatin (Eloxatin®) plus 5-fluorouracil and leucovorin (folinic acid)
- Oxaliplatin plus capecitabine (Xeloda®)

For squamous cell cancers several tested regimens are available including

- Cisplatin or carboplatin plus a taxane (paclitaxel or docetaxel)
- Cisplatin, or docetaxel, and 5-fluorouracil (5-FU)
- Cisplatin plus gemcitabine
- Oxaliplatin (Eloxatin®) plus 5-fluorouracil and leucovorin (folinic acid)

For neuroendocrine cancers several tested regimens are available including

- Cisplatin or carboplatin plus etoposide
- Carboplatin plus paclitaxel and etoposide
- Temozolomide plus capecitabine

For sarcomas (see sarcoma section).

Biological, Targeted, Immune Therapy and Supportive Therapy

Increasing evidence shows that patients with MSI/MMR-deficient, TMB-high or PD-L1-high unfavorable CUP may receive immune checkpoint inhibitor treatment in the second line. Recent data showed in fact that second-line immune checkpoint inhibitor treatment results in an overall response rate of approximately 20%.

Whether targeted agents should be used or not in patients with CUPs is still unknown. No validated actionable targets have emerged so far.

Therefore, participation in clinical trials evaluating targeted agents or combinations should be strongly encouraged.

Finally, for these patients both an effective psychosocial support and symptoms management and palliative care interventions are essential.

Key Take Home Messages

- Prevention includes adhering to sensible life-style factors and attending prescribed screening programs.
- Early recognition of vague symptoms as being a possible presentation of CUP.
- Cancers of unknown primary (CUP) is a distinct oncological entity, characterized by the presence of disseminated disease at presentation with the absence of an identifiable primary.
- Diagnosis is one of exclusion, following careful physical, pathological, and radiological examinations, with strong recommendations for discussion at a specialist multidisciplinary meeting. Therefore, careful pathology and radiology review is key to identifying potential primary tumor site of more favorable subtypes of CUP where site-specific therapy is indicated.
- Platinum-based doublet systemic chemotherapy remains the standard treatment for poor prognostic CUP.
- The role of more advanced diagnostic tests, such as molecular profiling, including next generation sequencing, is being evaluated as evolving evidence suggest potential benefit of more targeted treatments in subgroups of patients in whom a targetable mutation is identified.
- Increasing evidences that patients with MSI/MMR-deficient, TMB-high, or PD-L1-high unfavorable CUP may receive immune checkpoint inhibitor treatment in the second line.
- There is missing high-level evidence that gene expression profiling-directed therapy provides better patient outcomes.
- Participation in clinical trials should be considered for suitable candidates, and supportive services such as palliative care and psychological support are also essential in the management of these patients.

Areas for Further Research

- Better elucidation of early circulating biomarkers of CUPs.
- There is a need for better understanding of the etiology and risk factors for CUP.
- Inclusion in clinical trials in strongly encouraged to perform novel extensive genetic analysis.

Trusted Websites for Further Reading

https://www.cancer.org/cancer/cancer-unknown-primary/about/cancer-of-unknown-primary.html

https://www.who.int/activities/preventing-cancer

https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/preventable-cancers#heading-Zero

https://www.cancer.org/cancer/cancer-unknown-primary/about/cancer-of-unknown-primary.html

https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

https://www.annalsofoncology.org/article/S0923-7534(22)04769-X/fulltext

Bibliography

Chantal, P., Bochtler, T., Mileshkin, L. et al. (2021 May). A challenging task: identifying patients with Cancer of Unknown Primary (CUP) according to ESMO guidelines: the CUPISCO trial experience. *Oncologist* 26 (5): e769–e779.

Ciprian, T., Zaharie, F., Muresan, M.-S. et al. (2017 March). Mihnea Zdrenghea how to diagnose and treat a cancer of unknown primary site. *J Gastrointestin Liver Dis* 26 (1): 69–79.

Conway, A.M., Mitchell, C., Kilgour, E. et al. (2019 January). Molecular characterisation and liquid biomarkers in Carcinoma of Unknown Primary (CUP): taking the 'U' out of 'CUP'. *Br J Cancer* 120 (2): 141–153. doi: 10.1038/s41416-018-0332-2. Epub 2018 Dec 23. PMID: 30580378; PMCID: PMC6342985.

Elie, R., Assi, T., and Pavlidis, N. (2020a April). Exploring the biological hallmarks of cancer of unknown primary: where do we stand today? *Br J Cancer* 122 (8): 1124–1132.

Elie, R., Parent, P., Lefort, F. et al. (2020b March). New rising entities in cancer of unknown primary: is there a real therapeutic benefit? *Crit Rev Oncol Hematol* 147: 102882.

Elie, R. and Pavlidis, N. (2020a September). The diagnostic challenges of patients with carcinoma of unknown primary. *Expert Rev Anticancer Ther* 20 (9): 775–783.

Elie, R. and Pavlidis, N. (2020b September). Progress in refining the clinical management of cancer of unknown primary in the molecular era. *Nat Rev Clin Oncol* 17 (9): 541–554.

Fizazi, K., Maillard, A., Penel, N. et al. (2019). LBA15_PR - A phase III trial of empiric chemotherapy with cisplatin and gemcitabine or systemic treatment tailored by molecular gene expression analysis in patients with carcinomas of an unknown primary (CUP) site (GEFCAPI 04). *Ann Oncol* 30 (Supplement 5): v851.

Hainsworth, J.D., Rubin, M.S., Spigel, D.R. et al. (2013 January 10). Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research institute. *J Clin Oncol* 31 (2): 217–223. doi: 10.1200/JCO.2012.43.3755. Epub 2012 Oct 1. PMID: 23032625.

Hayashi, H., Kurata, T., Takiguchi, Y. et al. (2019 March 1). Randomized phase II trial comparing site-specific treatment based on gene expression profiling with Carboplatin and Paclitaxel for patients with Cancer of Unknown Primary site. *J Clin Oncol* 37 (7): 570–579. doi: 10.1200/JCO.18.00771. Epub 2019 Jan 17. PMID: 30653423.

Hayashi, H., Takiguchi, Y., Minami, H. et al. (2020). Site-specific and targeted therapy based on molecular profiling by next-generation sequencing for cancer of unknown primary site: a nonrandomized phase 2 clinical trial. *JAMA Oncol* 6: 1931–1938.

Lee, M.S. and Sanoff, H.K. (2020 December). Cancer of unknown primary. *BMJ* 7 (371): m4050.

Moran, S., Martínez-Cardús, A., Sayols, S. et al. (2016 October). Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis. *Lancet Oncol* 17 (10): 1386–1395. doi:10.1016/S1470-2045(16)30297-2. Epub 2016 Aug 27. PMID: 27575023.

National Cancer Intelligence Network. (2014). *Routes to diagnosis: cancer of unknown primary – NCIN data briefing*. http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis_cancer_of_unknown_primary

Panagiota, E., Mountzios, G., Pavlidis, N., and Pentheroudakis, G. (2015 July). Cancer of Unknown Primary origin in the genomic era: elucidating the dark box of cancer. *Cancer Treat Rev* 41 (7): 598–604.

Pavlidis, N., Khaled, H., and Gaafar, R. (2018). A mini review on cancer of unknown primary site: a clinical puzzle for the oncologists. *J Adv Res* 6: 375–382.

Shumei, K., Alsafar, A., Walavalkar, V. et al. (2021 May). Cancer of unknown primary in the molecular era. *Trends Cancer* 7 (5): 465–477.

Sora, K., Jeong, J.H., Yoon, S. et al. (2021 November 29). Real-world data analysis of patients with cancer of unknown primary. *Sci Rep* 11 (1): 23074.

Tanizaki, J., Yonemori, K., Akiyoshi, K. et al. (2022 February). Open-label phase II study of the efficacy of nivolumab for cancer of unknown primary. *Ann Oncol* 33 (2): 216–226. doi: 10.1016/j.annonc.2021.11.009. Epub 2021 Nov 26. PMID: 34843940.

Tilmann, B., Löffler, H., and Alwin, K. (2018 May). Diagnosis and management of metastatic neoplasms with unknown primary. *Semin Diagn Pathol* 35 (3): 199–206.

26 Diagnosis and Management of Gastrointestinal Lymphomas

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[Aspects of disease affecting the small bowel are also covered briefly in Chapter 8].

Introduction

Primary lymphoma of the gastrointestinal (GI) tract constitutes around 1–4% of all gastrointestinal malignancies (Ghimire et al. 2011). It represents 30–40% of extranodal lymphomas and accounts for 10–15% of all non-Hodgkin lymphomas (NHL) (Bautista-Quach et al. 2012). The most involved site is the stomach, followed by the small intestines, cecum, colon, and rectum (Ferreri and Montalbán 2007). Majority of the primary gastrointestinal lymphomas are mature B cell lymphomas, of which diffuse large B cell lymphomas (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphomas are the two most common histologic subtypes. Other mature B cell lymphomas in the GI tract include Burkitt lymphoma (BL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and Epstein–Barr virus-positive mucocutaneous ulcer (EBVMCU).

T cell and NK/T-cell lymphomas are less frequent. Intestinal T cell lymphoma have two distinct subtypes. Enteropathy-associated T cell lymphoma (EATL) is closely associated with celiac disease and more commonly found in individuals of northern European origin, while monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) shows no association with Celiac disease and is relatively increased in Asian and Hispanic populations (Swerdlow et al. 2016). Extranodal NK/T cell lymphoma (ENKTL) of the GI tract is strongly associated with Epstein-Barr virus (EBV) infection and usually carries a poor prognosis (Kim et al. 2013). NK-cell enteropathy (NKCE) or lymphomatoid gastropathy (LyGa) and indolent T cell lymphoproliferative disorder (ITLPD) of the gastrointestinal tract can also be found.

Clinical Presentations

Clinical symptoms of gastrointestinal lymphomas are usually vague and nonspecific, which depend on the site of lymphoma involvement and vary between individuals. The most common presenting symptoms include dyspepsia, abdominal pain, nausea, anorexia, diarrhea, weight loss, malabsorption, obstruction, and anemia (Bautista-Quach et al. 2012). Gastric ulcer, intestinal perforation, and intussusception have also been reported (England et al. 2012; Ferreri and Montalbán 2007; Ioannidis et al. 2011).

B Cell Lymphoma

Diffuse Large B Cell Lymphoma (DLBCL)

DLBCL is the most common type of lymphoma of the GI tract and represents 38–57% of primary GI lymphomas (Lewis et al. 2014). It might arise *de novo* or evolve from transformation of a low-grade B cell lymphoma, such as MALT lymphoma. The most common site of involvement of GI DLBCL is the stomach. GI tract DLBCL most often affects older males with a median age ranging between 50 and 60 years (Ferreri and Montalbán 2007). It is an aggressive lymphoma and patients usually present with a rapidly growing abdominal mass.

Pathogenesis

Several risk factors have been suggested for the pathogenesis of GI DLBCL. It has been reported that atrophic gastritis, especially when associated with immunodeficiency conditions, may play a role in the development of gastric DLBCL (Freeman et al. 1972). It is still controversial whether *H. pylori* is important for DLBCL pathogenesis. It was originally thought that DLBCL evolved from MALT is independent of *H. pylori* status, as it fails to respond to antibiotic therapy. However, other studies have found that MALT-evolved gastric DLBCL is associated with *H. pylori* infection and can respond effectively to *H. pylori* eradication, especially during early disease stages (Chen et al. 2001; Morgner et al. 2001). De novo DLBCL has also been reported to correlate with *H. pylori* status (Kuo et al. 2014). GI tract DLBCL is also common in patients with solid organ transplantation (Thomas et al. 1991).

Histopathology

As its name indicates, DLBCL is characterized by diffuse proliferation of large atypical lymphoid cells. The nuclei of the tumor cells should be equal or larger than the nuclei of benign

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histiocytes in the same tissue and are typically round, or slightly irregular with vesicular nuclear chromatin and prominent nucleoli (Figure 1). Several DLBCL morphological variants have been described including the centroblastic, immunoblastic, and anaplastic variants. The tumor cells express pan B cell markers such as CD19, CD20, CD22, PAX5. KI67 immunostaining usually demonstrates a high proliferation index. Immunophenotypic analysis can also help to predict prognosis, which will be discussed later.

Genetic Abnormalities

Immunoglobulin gene rearrangements are usually detectable. DLBCL is associated with several well-characterized chromosomal translocations. Around 30% cases harbor translocations involving *BCL6* gene at the chromosome 3q27 locus (Offit et al. 1994). The translocation partner is most often the *IGH* genes on chromosome 14q32, but could be other loci too. Translocation of the *BCL2* gene is observed in 20–30% DLBCL cases (Kramer et al. 1998). *MYC* translocation also occurs in 10–15% of DLBCL cases and often coexist with other

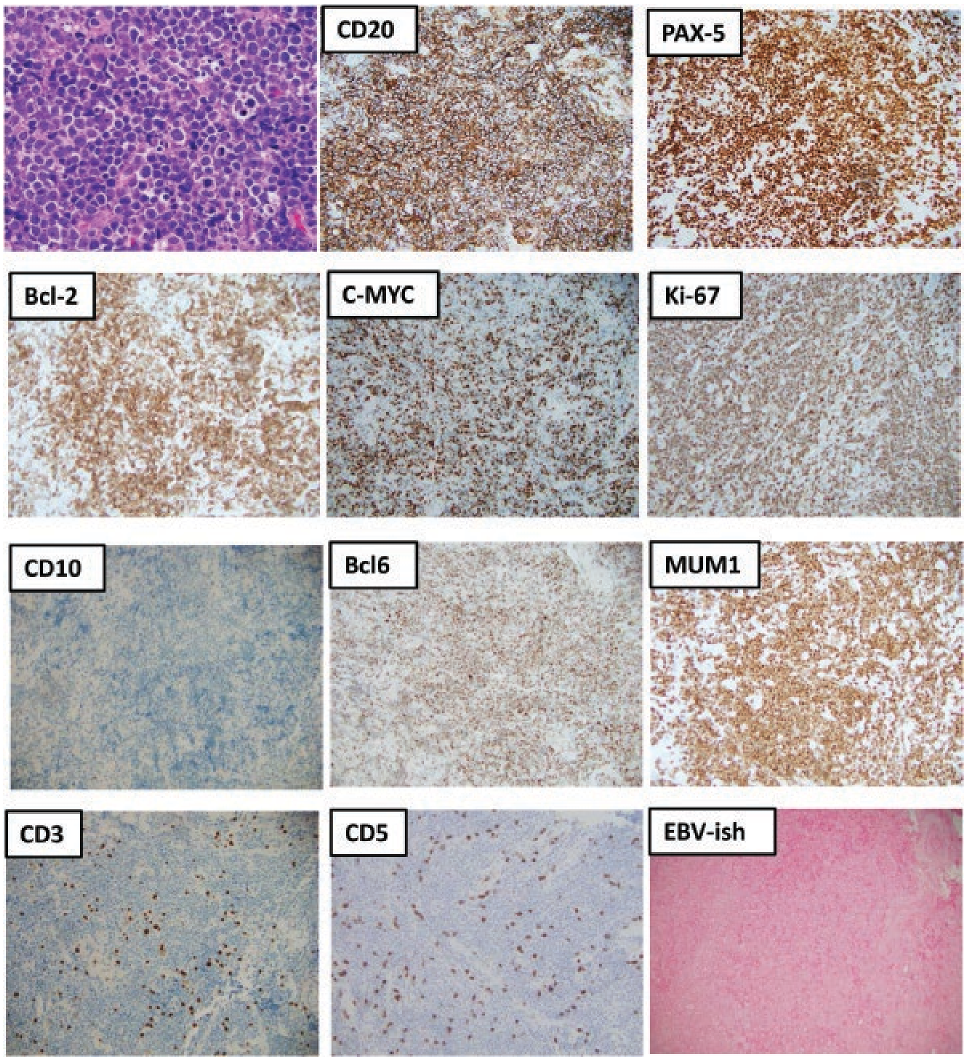

Figure 1 **Gastric DLBCL**. The H&E-stained sections of gastric mass demonstrate sheets of polymorphic large atypical lymphoid infiltrate into the gastric mucosa. Under high power, the large, atypical cells have moderate to abundant eosinophilic cytoplasm, round to irregular nuclear contour, vesicular or dispersed nuclear chromatin and variable nucleoli. Scattered small mature lymphocytes and cellular debris are seen in the background. There are also brisk mitotic activities as well as apoptotic cells. The atypical cells are diffusely positive for B-cell markers (CD20 and PAX-5) with co-expression of Bcl-2, Bcl-6, MYC, and MUM-1, and are negative for CD5, CD10, CD138, CyclinD1, and CD30. The reactive non-neoplastic T-cells in the background are positive for T-cell markers (CD3 and CD5). The neoplastic lymphoid cells show high proliferation index with 70–80% of cells positive for Ki-67. The findings are diagnostic for diffuse large B-cell lymphoma, nongerminal center type, double expressor BCL2+/MYC+.

translocations (Barrans et al. 2010). The 2016 WHO classification included the lymphoma with *MYC* rearrangement and another oncogene rearrangement (*BCL2* and/or *BCL6*) in a new category designated as high-grade B-cell lymphoma with *MYC, BCL2*, and/or *BCL6* rearrangements, also known as "double-hit" (or "triple hit") lymphoma. Double-hit lymphomas are aggressive and warrant a more aggressive treatment (Swerdlow et al. 2016).

DLBCL can be divided into germinal center B-cell (GCB) type and activated B-cell (ABC) type based on their gene expression profiles (Alizadeh et al. 2000). Patients with GCB type DLBCL had a better overall survival than those with ABC type DLBCL (Alizadeh et al. 2000; Rosenwald et al. 2002). As traditional gene expression profile methods are not widely used for daily diagnostic practice, several immunohistochemical algorithms have been developed to be used as surrogates to predict cell-of-origin for lymphoma cells. The most commonly used one is the Hans Algorithm, which classifies DLBCL cases into GCB and non-GCB type based on the IHC results of CD10, BCL6, and MUM1/IRF4, and had a 76% concordance with cell-of-origin detected by GEP (Hans et al. 2004).

Mutations in many genes have been reported in DLBCL. Interestingly, the frequency of specific mutations is related to the tumor cell of origin subtype. For example, *EZH2* and *GNA13* mutations are almost only seen in the GCB subtype, while *CARD11*, *MYD88*, and *CD79B* mutations are commonly seen in the ABC subtype (Swerdlow et al. 2017).

Treatment and Prognosis

Patients with GI DLBCL have variable outcomes. Several factors have been suggested to stratify the prognosis. First, disease stage and patient age are closely associated with survival. Other factor associated with inferior outcome include tumor bulk, elevated LDH, male sex, Vitamin D deficiency, low body mass index, elevated serum free light chains, monoclonal serum IgM proteins, low absolute lymphocyte/monocyte count, and concordant bone marrow involvement (Swerdlow et al. 2017). International Prognostic Index or IPI uses some of these factors to risk stratify these patients. As we have discussed before, genetic markers are also being used to predict the outcome of DLBCL patients.

The Lugano modification of the Ann Arbor system is usually used for staging of GI lymphoma (Table 1) (Rohatiner et al. 1994). The mainstay of therapy for DLBCL is chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). Patients with high-grade B Cell Lymphoma, previously referred to as "Double-Hit DLBCL" are treated with more intense regimens like Dose Adjusted R-EPOCH (Rituxan, etoposide, vincristine, doxorubicin, prednisone, and cyclophosphamide).

For patients with limited stage of GI DLBCL, R-CHOP may be administered alone or may be given with radiation therapy (RT) as combined modality therapy (CMT). Radiation is generally incorporated if a patient has received abbreviated number of chemotherapy cycles or attained a partial response to the planned treatment provided radiation toxicity is not deemed excessive to the patient.

Patients with advanced stage disease receive six cycles of R-CHOP in most settings but occasionally up to eight cycles can be considered. Some experts omit or dose reduce vincristine given the risk of perforation. But in our opinion, perforation is unpredictable and may happen at any stage of the

Table 1 Lugano staging for GI tract lymphoma Adapted from (Rohatiner et al. 1994).

Stage	Involvement
Stage I	Tumor confined to the gastrointestinal tract, e.g. stomach Single primary site, or multiple noncontiguous lesions
I1	Tumor infiltration limited to mucosa and/or submucosa
I2	Tumor infiltration into muscularis propria and/or subserosa and/or serosa
Stage II	Tumor extending into abdomen from primary GI site Nodal involvement
II1	Local perigastric nodes in gastric lymphoma mesenteric in small and large bowel lymphoma
II2	Distant mesenteric in gastric lymphoma para-aortic, para-caval, pelvic, inguinal
Stage IIE	Penetration of serosa with involvement of adjacent organs/tissues
Stage IV	Disseminated extranodal involvement, e.g. localization in bone marrow, liver etc., or a gastric/bowel lesion with supradiaphragmatic nodal involvement

treatment. We therefore do not routinely omit it from the first cycle of chemotherapy.

Role of central nervous system (CNS) prophylaxis is better defined for higher grade lymphomas like Burkitt's or High-Grade B cell Lymphomas with Genetic Rearrangements. We reserve CNS prophylaxis for patients with DLBCL who have involvement of multiple extranodal sites or high-risk areas like testicles, sinuses, or paraspinal structures. CNS IPI is useful in assessing the risk of CNS involvement and prophylaxis may be offered to those deemed higher risk. Combination of intrathecal chemotherapy and intravenous drugs that cross the blood brain barriers like methotrexate and cytarabine may be incorporated in the standard treatment for this purpose.

Autologous stem cell transplant is generally offered to fit patients who have relapsed /refractory disease that has demonstrated chemosensitivity to second line regimens. However, multiple new regimens and novel combinations are being used in this space. Role of CD19-specific autologous chimeric antigen receptor (CAR) -T cell is an evolving concept but is currently approved for patients who have been failed by two prior lines of chemotherapy.

Extranodal Marginal Zone Mucosa-associated Lymphoid Tissue (MALT) Lymphoma

MALT lymphoma represents 7–8% of all B cell lymphomas. It mainly involves the stomach, although any parts of the GI tract can be affected. Gastric MALT lymphoma constitutes nearly 50% of gastric lymphomas (Psyrri et al. 2008), and mainly occurs in older patients with the peak incidence between the age of 50 and 60 years. Recently the incidence has increased significantly in patients older than 40 (Violeta Filip et al. 2018). Patients usually present with nonspecific symptoms including gastroesophageal reflux, epigastric pain/discomfort, anorexia, weight loss, or occult gastrointestinal bleeding. The endoscopic features of the disease vary and might present as erosions, ulcers, superficially depressed (early cancer-like) lesions, or protrusions (Inagaki et al. 2004).

Pathogenesis

MALT lymphoma is an indolent B-cell neoplasm developing from lymphoid populations induced by chronic inflammation (Sagaert et al. 2010). *Helicobacter pylori* infection is as an important etiologic factor and found in over 90% cases of gastric MALT lymphoma (Stolte et al. 2002). It has been reported that the neoplastic proliferation of lymphoma cells depends on the antigen-driven T cells specific for the *H. pylori* organism (Hussell et al. 1993). And the fact that eradication of *H. pylori* could cause MALT regression further supported the role of *H. pylori* in MALT lymphoma-genesis (Wotherspoon et al. 1993).

Besides *H. pylori* infection, chromosomal translocations have also been implicated in the development and progression of MALT lymphoma independently of chronic inflammation (Troppan et al. 2015).

Histopathology

MALT lymphoma is a lymphoma of mature B lymphocytes with destructive growth pattern. The lymphoma cells are heterogeneous, predominantly small to medium-sized lymphoid cells (Figure 2). Some lymphoma cells are centrocyte-like with slightly irregular nuclei, moderately dispersed chromatin; while others have accumulation of abundant pale cytoplasm which lead to a monocytoid appearance. Plasmacytic differentiation might also be present (Swerdlow et al. 2017). One of the diagnostic features of MALT lymphoma is lymphoepithelial lesions (LEL), the infiltration and disruption of epithelial structures by aggregates of >3 neoplastic lymphoid cells. The lymphoma cells might also infiltrate and disrupt reactive germinal center in a marginal zone distribution, leading to "moth-eaten" appearance.

The neoplastic cells of MALT lymphoma typically express IgM, and occasionally IgA or IgG, with light chain restriction. They are positive for CD20, CD79a, and typically negative for CD5 and CD10, although rare cases of CD5+ MALT lymphoma have been reported (Jaso et al. 2012). CD43 and BCL2 might be aberrantly expressed by the lymphoma cells in up to 50% cases (Psyrri et al. 2008).

Genetic Abnormalities

Balanced translocations have been reported for MALT lymphoma, including t(11;18)(q21;q21), t(14;18) (q32;q21), t(1;14) (p22;q32), and t(3;14)(p14;q32) translocations. The t(11;18) (q21;q21) translocation is the most common translocation, and occurs in 30–40% of gastric MALT lymphoma. It results in the chimeric fusion transcript of N-terminal API2 with three intact baculovirus inhibitor of apoptosis repeat (BIR) domains and the C-terminal MALT1 region containing an intact caspase-like domain (Kramer et al. 1998). Notably, the t(11;18)(q21;q21) translocation has been associated with cases not responsive to *H. pylori* eradication (Alizadeh et al. 2000). The t[14;18] [q32;q21], t[1;14] [p22;q32], and t[3;14] [p14;q32] translocations result in the transcriptional deregulation of MALT1, BCL10, and FOXP1, respectively. All these translocations can activate the nuclear factor κB (NF-κB) oncogenic pathway, which in turn leads to lymphomagenesis (Psyrri et al. 2008).

Treatment and Prognosis

MALT lymphoma is an indolent disease and slow to disseminate. For *H. pylori*-positive MALT lymphoma in the early stage, the first line of therapy is the eradication of HP, by combining a proton pump inhibitor (PPI) with 2 to 3 antibiotics. Complete remission of the early-stage MALT lymphoma was found in 75–80% of patients who had successful *H. pylori* eradication (Bautista-Quach et al. 2012). This may take several months, and it is important to not switch lines of therapy unless there is

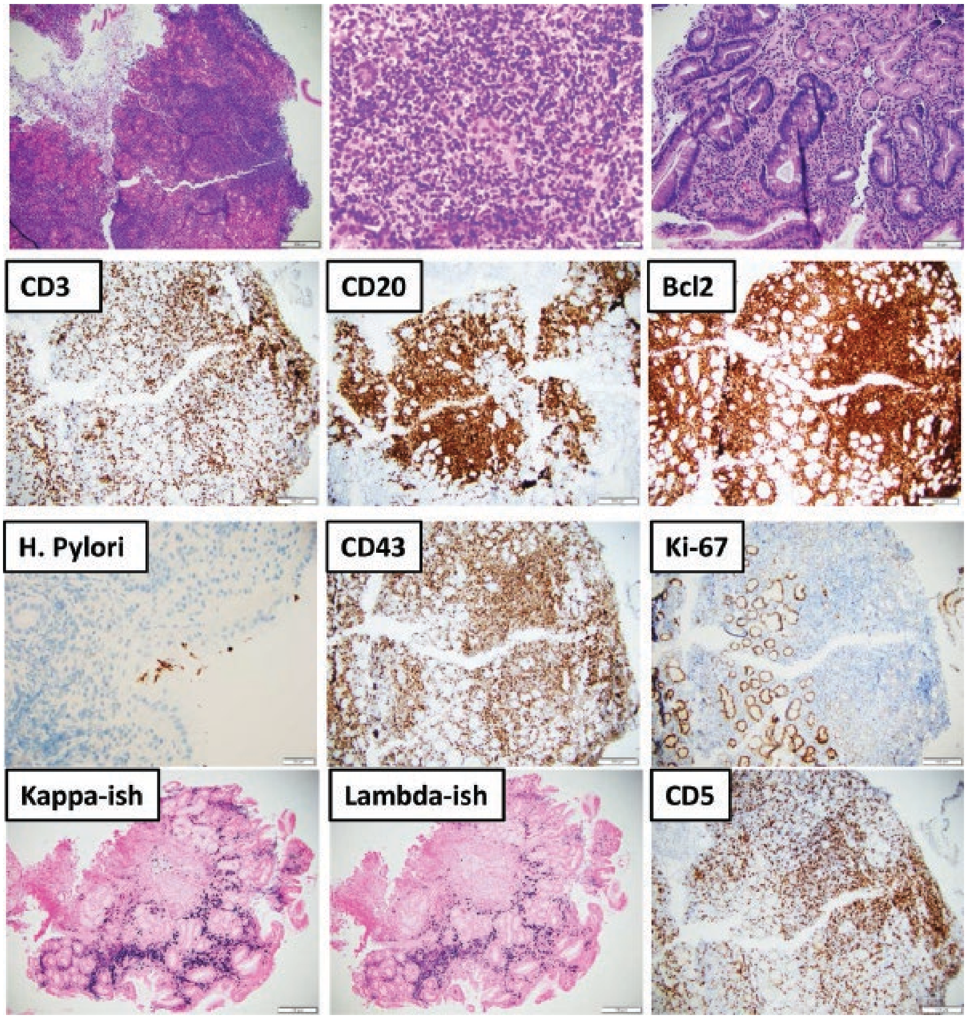

Figure 2 Early stage extranodal marginal zone lymphoma (Maltoma). The gastric biopsy shows dense atypical lymphoid infiltrate in a background of Helicobacter gastritis with focal intestinal metaplasia. The lymphoid cells are predominant small mature lymphocytes intermixed with scattered plasmas cells. By immunohistochemistry, the lymphoid infiltrates are strongly positive for B-cell marker (CD20+) with aberrant coexpression of Bcl2 and CD43 and are negative for CD5 and cyclin D1. CD3 and CD5 stains highlight reactive T-cells in the background. The cell proliferation index Ki-67 is relatively low (<5%) in lymphoid cells. Kappa/lambda in situ hybridization highlights reactive polytypical plasma cells. In addition, B-cell clonality analysis (*IgH* gene rearrangement) by PCR is positive (not shown).

overt progression. However, patients with the t(11;18)(q21;q21) translocation have a lower chance of responding to *H. pylori* eradication therapy, hence may be considered for radiation upfront. Nevertheless, *H. pylori* eradication is still used for the initial management of these patients due to the low toxicity and chance of effectiveness in a subset of the patients.

For patients in advanced stages, adjuvant antitumor therapy, similar to any low-grade lymphoma, is also indicated if they have symptoms from the disease, or if it threatens functionality of a vital structure. Therapies that are more commonly used incorporate Rituximab alone or in combination with other chemotherapeutics like bendamustine. R-CHOP is generally reserved for patients who have undergone large cell transformation or there is a high clinical suspicion of it. Rituximab maintenance may improve progression-free survival and is offered to most patients except those who have received bendamustine with rituximab given lack of clear benefit in this setting.

For patients with early-stage *H. pylori*-negative MALT lymphoma, local radiation therapy administered with curative intent is usually recommended due to the high response rate. For patients with advanced disease, treatment is postponed until symptoms develop.

Immunoproliferative Small Intestinal Disease (IPSID)

IPSID is also known as alpha heavy chain disease (αHCD). It is a variant form of MALT lymphoma of the small intestine which secrets defective immunoglobulin alpha heavy chain (Al-Saleem and Al-Mondhiry 2005). IPSID usually involves a young patient population, with peak incidence between the age of 20 and 30. It is most prevalent in the Mediterranean basin, the Middle East, and Africa, and is associated with factors of low socioeconomic status (Al-Saleem and Al-Mondhiry 2005). Typical clinical presentations include malabsorption, diarrhea, abdominal pain, wasting, fever, and steatorrhea.

Pathogenesis

Similar to *H. pylori* associated gastric MALT lymphoma, chronic infection is also believed to play an important role in the pathogenesis of IPSID. *Campylobacter jejuni* infection has been reported to be associated with IPSID and early-stage disease responds to antibiotics with 30–70% complete remission rate (Al-Saleem and Al-Mondhiry 2005; Lecuit et al. 2004). The continuous antigenic stimulation due to *C. jejuni* infection might lead to sustained stimulation of B cells which results in the neoplastic progression.

Histopathology

IPSID is characterized by heavy lymphoplasmacytic infiltration in the lamina propria of small bowel. LEL lesions might be present. The associated histopathological changes vary and range from small atypical lymphoid aggregation to DLBCL. Both atypical lymphoid cells and plasmacytic population express monoclonal cytoplasmic alpha chain without light chains.

Genetic Abnormalities

IPSID usually harbors deletions of the *IGHA* gene which results in the expression of defective heavy chain protein and prevents the binding of light chain to form an intact immunoglobulin molecule. Cytogenetic abnormalities are rarely reported.

Treatment and Prognosis

Untreated IPSID usually progresses relentlessly and can cause severe malabsorption and malnutrition. Early stage IPSID can be treated with antibiotics with 30–70% complete remission (Al-Saleem and Al-Mondhiry 2005). Patients who do not respond to antibiotics therapy or patients who present with advanced stage disease should be treated with chemotherapy (Al-Saleem and Al-Mondhiry 2005).

Burkitt Lymphoma (BL)

BL is a highly aggressive B cell lymphoma with three distinct clinical forms: endemic BL, which occurs mainly in Africa and is associated with EBV infection; sporadic BL, which happens mainly in children and young adults and is seen throughout the world; and immunodeficiency-associated BL, which is often seen in the setting of HIV infection (Swerdlow et al. 2017). Extranodal involvement is common and GI tract is frequently involved. Most sporadic BL cases present with abdominal masses, commonly in the ileocaecal region.

Pathogenesis

BL development depends on the constitutive expression of *MYC*, which is a transcription factor that controls the expression of many target genes and thus regulates various cell processes including cell growth, division, and apoptosis. All three variants of BL harbor the characteristic translocation involving the *MYC* gene.

Histopathology

BL typically shows diffuse infiltration of monotonous medium-sized lymphoid cells with round to oval nuclei, multiple small nucleoli, and scanty cytoplasm which usually contains lipid vacuoles (Figure 3). The lymphoma has high rates of both proliferation and apoptosis. Frequent mitotic figures can be seen, and the tangible body macrophages containing apoptotic body can deliver the characteristic “starry sky” morphology.

The lymphoma cells typically express B-cell markers (CD19, CD20, CD79a, and PAX5), germinal center markers (CD10 and BCL6), and demonstrate light chain restriction. Almost all cases have strong expression of MYC protein. The proliferation index is very high with nearly 100% KI-67 staining.

Genetic Abnormalities

The molecular hallmark of BL is the translocation of *MYC* gene at 8q24, most frequently to the immunoglobulin heavy (*IgH*) chain gene at 14q32, and less commonly to the *Ig kappa (IgK)* locus at 2p12 or *Ig lambda (IgL)* locus at 22q11. Other chromosomal abnormalities might also happen, including gains of 1q, 7, 12 and losses of 6q, 13q32-34, and 17p (Swerdlow et al. 2017).

Treatment and Prognosis

BL is an extremely aggressive disease and fatal if left untreated. Treatment should be started within 48 hours and patients are usually treated with intensive, frequent multiagent therapy with adequate CNS prophylaxis. All patients should be screened for CNS involvement upfront regardless of presence of signs and symptoms. There are three main treatment approaches: 1) intensive, short-duration combination chemotherapy (e.g., R-CODOX-M/IVAC, CALGB 9251); 2) Long duration ALL-like therapy with a stepwise induction, consolidation, and maintenance therapy (e.g., CALGB 8811 regimen, R-HyperCVAD); and 3) Infusional chemotherapy with dose-adjusted EPOCH plus rituximab. Most of these regimens have drugs that cross the blood brain barrier and some make provisions for extra CNS-directed treatment in patients with confirmed CNS disease at the time of presentation.

For patients with HIV-related Burkitt’s Lymphoma, viral control is extremely important. We initiate HIV-directed treatments promptly in patients with a new diagnosis of HIV and work with

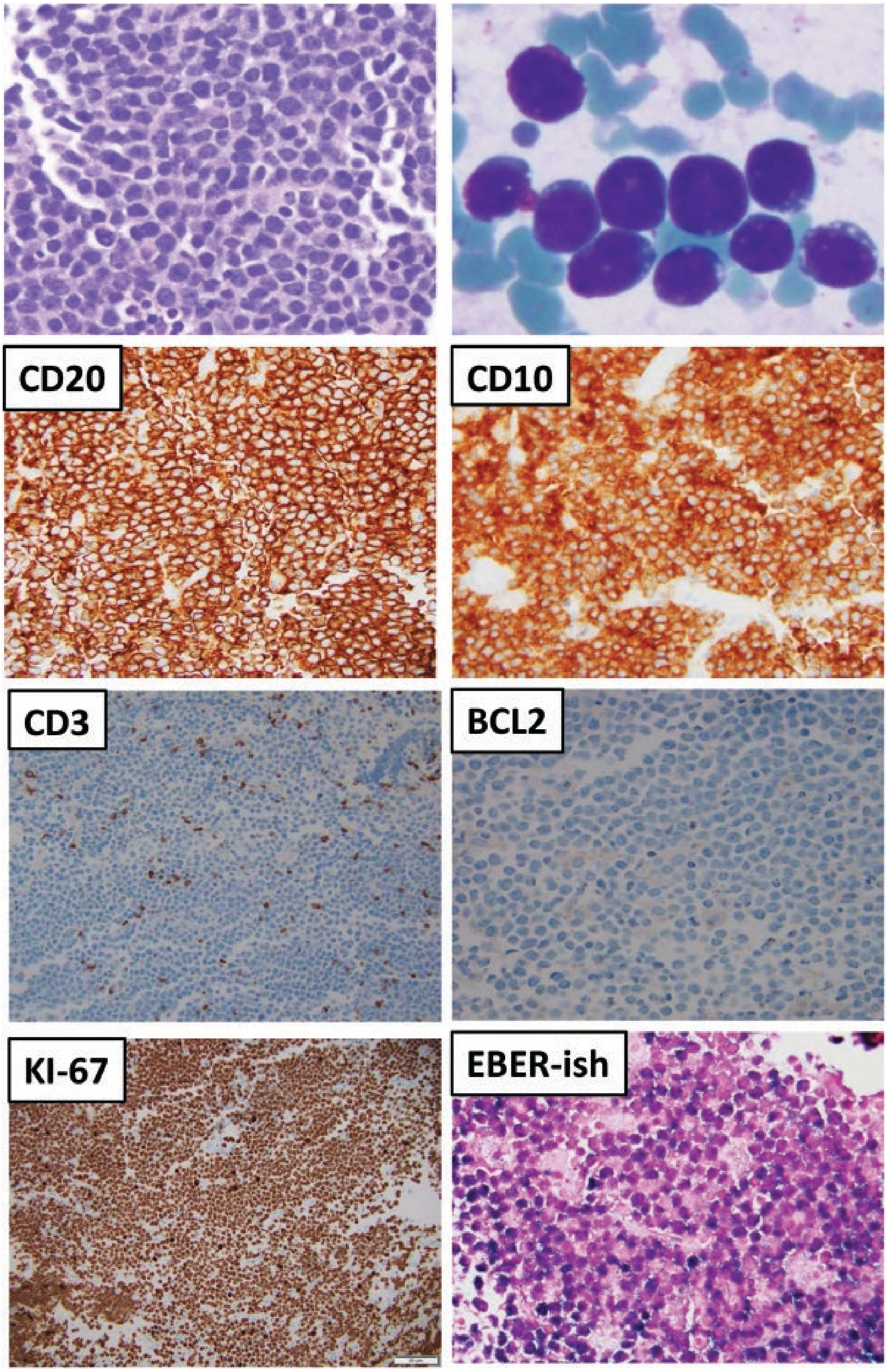

Figure 3 Colon Burkitt lymphoma. The biopsy of colon mass shows diffuse atypical lymphoid infiltrate with sheets of medium sized cells with high N/C ratio, vesicular chromatin, inconspicuous nucleoli, and cytoplasmic vacuoles. There are many apoptotic cells and occasional mitotic figures. Ki-67 staining highlights a very high proliferation index of around 100%. The tumor cells are diffusely positive for c-MYC (not shown), and negative for Bcl-2. EBV-encoded RNA (EBER) in situ hybridization (ISH) is positive.

an HIV expert to help control the viral load better in those with a known diagnosis. Most centers prefer to use R-CODOX-M/IVAC. DA R-EPCOH may be considered in cases where CNS involvement is not a major consideration. Rituxan is seldom omitted from upfront treatment for CD20-positive cases. We would certainly add Rituxan if CD4 count is greater than 50 /microliter and strongly consider it in patients who have recently been started on anti-retroviral therapy where we anticipate CD4 recovery swiftly.

Patients with primary refractory disease or those who relapse early have poor outcomes and should be considered for clinical trials when available.

Follicular Lymphoma (FL)

FL is a neoplasm of germinal center B cells which usually displays a follicular pattern. It is the second most common type of non-Hodgkin lymphoma of adults, predominantly involving lymph nodes. The gastrointestinal tract is the most common extranodal site of involvement. Most cases of primary GI tract follicular lymphoma occur in the small intestine, especially the duodenum. It has distinctive features and has been classified as a variant of follicular lymphoma (duodenal-type follicular lymphoma) (Swerdlow et al. 2016).

Pathogenesis

The presence of antigen stimulation has been proposed to affect the pathogenesis of intestinal follicular lymphoma. However, no clear pathogen has been identified thus far (Iwamuro et al. 2016). It has been reported that in *H. pylori*-positive intestinal FL cases, eradication of *H. pylori* resulted in lymphoma regression (Hayashi et al. 2013; Toyoda et al. 2001). Interestingly, partial lymphoma regression has also been reported in *H. pylori*-negative cases after antibiotics treatment (Yaguchi et al. 2010).

Similar to nodal FL, GI tract FL also often has the hallmark t(14;18) (*IGH-BCL2*) translocation (Shia et al. 2002), which leads to the overexpression of Bcl-2 protein. Bcl-2 inhibits apoptosis by binding and neutralizing activated proapoptotic Bcl-2 family members, such as Bax and Bak, and in turn leads to enhanced cell survival.

Histopathology

GI tract FL consists of neoplastic follicles in the mucosa/submucosa. The follicles are composed of mainly monotonous small centrocytes admixed with variably numbers of centroblasts. Most of the cases are histologically Grade 1 to 2 (low grade). Infiltration of the lamina propria outside of the follicles can be seen. The lymphoma cells are usually positive for CD20, BCL2, and CD10.

Genetic Abnormalities

The lymphoma cells typically carry t(14;18) (q32;21), with rearrangement of the *BCL2* gene (Shia et al. 2002).

Treatment and Prognosis

GI tract FL has an excellent long-term survival, although there may be local re-occurrence (Mori et al. 2010; Schmatz et al. 2011). Therefore, a wait-and-watch approach is generally considered to be appropriate for cases of low tumor burdens. For patients with symptoms, treatment with adjuvant chemotherapy with rituximab, or rituximab alone may also be considered. Surgery is reserved for select cases and mostly does not have a role in this setting unless done for palliation. Choice of chemotherapy is based on principles similar to other low-grade lymphoma as mentioned under MZL above. However, Rituxan monotherapy has higher response rates in FL when compared to MZL.

Patients with an early relapse of follicular lymphoma are considered high risk if relapse occurs within two years of first-line treatment. These patients are considered for an autologous transplant provided their diseases remain sensitive to second-line chemotherapeutics and their health permits. Multiple small molecules like PI3 kinase inhibitors and immunomodulators like lenalidomide are being increasingly used for these patients. CD19-specific CAR-T cells were recently approved for relapsed/refractory follicular lymphoma patients who have been failed by at least two prior lines of chemotherapy treatments.

Mantle Cell Lymphoma (MCL)

Most MCL patients present with advanced-stage disease with extranodal involvement. GI tract is one of the most common extranodal sites of MCL. It was initially reported that around 20% MCL cases might have GI tract involvement (Romaguera et al. 2003). Further investigation revealed that GI tract involvement of MCL was up to over 80% microscopically (Salar et al. 2006). Primary GI MCL is rare with a frequency of 4–9% in all the GI B-cell lymphomas, and usually presents in the form of multiple lymphomatous polyposis (Ruskoné-Fourmestraux and Audouin 2010).

Pathogenesis

MCL has the characteristic t(11;14)(q13;q32) translocation, which involves *IGH* and *CCND1* genes and leads to cyclin D1 overexpression and cell cycle dysregulation (Li et al. 1999).

Histopathology

MCL of the GI tract usually shows infiltration of nodular lymphoid aggregates in the lamina propria or submucosa. The infiltration is mainly composed of uniform population of small to medium sized cells with irregular nuclei. The lymphoma cells express pan-B cell antigens such as CD20, CD79a, PAX5 and shows light chain restriction. They are usually positive for CD5 and CyclinD1, but lack CD10, BCL6, and CD23. SOX11 has been described as a diagnostic marker for MCL, especially for the CyclinD1-negative cases.

Genetic Abnormalities

As mentioned before, the hallmark of MCL is the t(11;14)(q13;q32) translocation. Other cell cycle regulators might also be affected. Rearrangement of *CCND2* (cyclin D2) has been reported in cyclin D1-negative cases (Salaverria et al. 2013).

MCL is also one of the B cell lymphomas with the highest degree of genomic instability, and carries a large number of secondary chromosomal alterations, including losses, gains, and amplifications of chromosomal regions that contain important genes involved in cell-cycle regulation, DNA damage response pathways and signal transduction. Copy-neutral loss-of-heterozygosity (LOH) also has been demonstrated. The most important LOH involves the chromosome 17p and is associated with *TP53* inactivation (Pérez-Galán et al. 2011).

Treatment and Prognosis

MCL has a variable course of disease. Blastoid and pleomorphic variants are considered particularly aggressive and presence of p53 mutation generally confers a poor outcome. While a small number of patients might have an indolent course and can live untreated for many years; for most patients, MCL is an aggressive lymphoma and should be treated with combination chemotherapy and immunotherapy at the time of diagnosis.

Practices vary across the country, but most centers use rituximab in combination with bendamustine or CHOP chemotherapy. Cytarabine has been incorporated with these regimens by several experts in an effort to improve response rates and perhaps progression-free survival. More intense regimens like Hyper-CVAD are used by select centers for younger patients with a good performance status.

Majority of these patients are offered a consolidative autologous transplant in first complete remission. Maintenance rituximab is offered to a sizable majority, especially those who have had a partial response, received an R-CHOP like regimen or are status post a consolidative autologous transplant.

Bruton Tyrosine Kinase (BTK) inhibitors are increasingly being used as second-line agents for these patients. Choice of agent is largely determined by the side effect profile; second generation BTK inhibitors are more selective, hence with less toxicity. Bortezomib, lenalidomide, and venetoclax have activity in relapsed refractory setting as well. CD19-specific CAR-T has been approved for use in patients with relapsed, refractory diseases. The sequence in which these therapies are used is variable and we recommend enrolling in a clinical trial when feasible.

Epstein–Barr Virus-positive Mucocutaneous Ulcer (EBVMCU)

EBVMCU is a newly recognized B cell lymphoproliferative disorder driven by latent EBV infection. It presents as discrete ulcerations in cutaneous and mucosal sites which most commonly involves oral cavity. Gastrointestinal tract involvement can be seen (19–40% colon, 30% esophagus, 20% rectum, and 10% terminal ileum). EBVMCU usually occurs in patients with various types of immunosuppression including primary, iatrogenic, or aging-induced (Dojcinov et al. 2010). Patients usually present with symptoms related to the ulcerated lesion, and systemic symptoms are rarely seen.

Pathogenesis

As its name indicates, EBVMCU is uniformly associated with EBV. It has been proposed that in immunosuppressed patients, EBV virus can only be maintained in a systemic dormant state by the host immune system. An additional site-restricted immune-modulating factor can disrupt the balance, thus facilitating the EBV-driven clonal proliferation of lymphocytes and subsequent transformation.

Histopathology

EBVMCU lesion shows ulceration with infiltration of large atypical lymphoid cells admixed with plasma cells, histiocytes, and eosinophils. The atypical lymphoid cells are variable in appearance and can resemble the tumor cells of diffuse large B-cell lymphoma (DLBCL) and classic Hodgkin lymphoma (cHL). Scattered apoptotic cells might be seen. Angioinvasion and necrosis might be present.

The large, atypical cells are usually positive for CD20, PAX5, OCT2, CD10, BCL6, CD30 and negative for MUM1. BOB1 expression is variable. EBV in situ hybridization is consistently positive. There are numerous background CD8+ T cells.

Genetic Abnormalities

It has been reported that less than half of the EBVMCU cases exhibited *IgH* gene rearrangements and some exhibited *TCR* gene rearrangements (Dojcinov et al. 2010). No specific genetic mutation has been reported for EBVMCU yet.

Treatment and Prognosis

EBVMCU is an indolent disease with a favorable prognosis. Most cases regress spontaneously or with reduction of immunosuppressive therapy. Occasional cases of relapsing/remitting course but without progression have been reported (Dojcinov et al. 2010).

T Cell Lymphoma

Enteropathy-associated T Cell Lymphoma (EATL)

Enteropathy-associated T cell lymphoma had been previously designated as type I EATL. It is a neoplasm of intraepithelial T cells in Celiac disease patients with an incidence of 0.22–1.9 cases per 100,000 in celiac population (Swerdlow et al. 2017). EATL is the most common primary intestinal T cell lymphoma in western countries (Delabie et al. 2011). It mainly occurs in older patients with peak incidence between 60 and 70 years of age and is localized primarily in the small intestine.

Patients usually present with gluten-insensitive malabsorption, diarrhea, and abdominal pain. Other symptoms include weight loss, anorexia, nausea, vomiting, and sometimes intestinal perforation/hemorrhage. Many patients are diagnosed with celiac disease at the time of presentation with EATL. History of childhood-onset celiac disease is uncommon.

Pathogenesis

EATL is a well-recognized complication of celiac disease, a common auto-immune disorder characterized by intolerance to dietary gluten and occurring more often in individuals with the human leukocyte antigen (HLA) class II haplotypes HLA-DQ2 or DQ8 (Swinson et al. 1983). Recent research suggested that there are two pathways of EATL lymphomagenesis. EATL might evolve from refractory celiac disease (RCD) II, which is characterized by aberrant intraepithelial lymphocyte immunophenotype and clonal *TCR* gene rearrangement analysis. It is known that IL-15 plays an important role in the pathogenesis of RCD II (Mention et al. 2003). EATL can also arise de novo in patients with uncomplicated celiac disease or RCD I. The detailed mechanism for de novo EATL is still unknown. Those patients usually have a better prognosis compared to the RCD II-derived EATL (Chander et al. 2018).

Histopathology

EATL shows infiltration of pleomorphic medium-sized to large cells with round or polygonal nuclei, distinct nucleoli, and moderate to abundant cytoplasm. There is often admixture of inflammatory cells, such as histiocytes, plasma cells, and eosinophils. Features of celiac disease, such as villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis etc., are usually observed in the adjacent intestinal mucosa. The lymphoma cells are positive for CD3, CD7, and CD103, but are typically negative for CD4, and CD5, and variably express CD8 and CD30. They may also express cytotoxic markers such as granzyme B, perforin, and TIA1.

Genetic Abnormalities

Almost all EATL cases have TRB or TRG clonal rearrangement. Most cases show chromosomal aberrations including gains at 9q34 region, or deletions in 16q12.1. EATL also often demonstrates gains at 1q and 5q (Delabie et al. 2011). Deletions or losses of heterozygosity (LOH) at chromosome 9p21, which harbors the tumor suppressor genes *CDKN2A* and *CDKN2B*, and loss of the 17p region, which contain the *TP53* gene, are also frequent in EATL (Obermann et al. 2004). Recurrent mutations in *JAK/STAT* and *RAS* signaling pathways have also been reported (Nicolae et al. 2016).

Treatment and Prognosis

Due to the association with celiac disease, EATL patients should be on a gluten-free diet. EATL is an aggressive disease with a poor prognosis. Surgery may have a palliative role in select cases. The 5-year survival was reported to be between 8% and 20% with most anthracycline-based regimens. However, better survival has been reported with aggressive therapies like Hyper-CVAD in case reports and series (Sieniawski et al. 2010). Patients who are candidates for autologous HCT may benefit from HCT in first remission. Checkpoint inhibitors are being tested in clinical trials for this group of patients as well. Other drugs of interest being tried in different combinations include agents like romidepsin, brentuximab, and campath. Given the rarity of the condition, there is no standard treatment at this time.

Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL)

Similar to EATL, MEITL is also a primary T cell lymphoma derived from intraepithelial lymphocytes. However, it is not associated with celiac disease. MEITL is seen more often in Asians and individuals of Hispanic descent. Males are more often affected than females with a male to female ratio of 2:1 (Alizadeh et al. 2000). Patient usually presents with nonspecific symptoms, such as abdominal pain, weight loss, diarrhea, etc. MEITL involves most often the small intestine, and occasionally the stomach and colon (Tse et al. 2012). Endoscopy findings have been reported as mosaic and diffuse mucosal thickening and edema, as well as shallow ulceration in the small intestine (Hong et al. 2016).

Pathogenesis

MEITL arises from intraepithelial T lymphocytes which acquire genetic abnormalities that promote their survival, proliferation, and lead to malignancy. The detailed genetic abnormalities will be discussed in the paragraphs below.

Histopathology

MEITL is characterized by monomorphic infiltration of medium-sized lymphoid cells with round nuclei, finely dispersed chromatin, and pale cytoplasm (Figure 4). There is prominent epitheliotropic infiltration. Unlike EATL, background inflammation and necrosis are usually absent. The lymphoma cells are positive for CD3, CD8, and CD56. Most tumor cells are CD5 negative, and express γδ T-cell receptor, suggesting a γδ T-cell origin (Chan et al. 2011).

Genetic Abnormalities

Most cases show TR clonal rearrangement. Similar to EATL, majority of the MEITL cases demonstrate chromosomal gains at 9q34 region (Deleeuw et al. 2007). But unlike EATL, MEITL also frequently shows gains of the *MYC* oncogene locus at 8q24 (Deleeuw et al. 2007), while gains at 1q and 5q are rarely seen (Deleeuw et al. 2007).

Several important genetic mutations have been identified in MEITL. The most commonly mutated genes include *SETD2*,

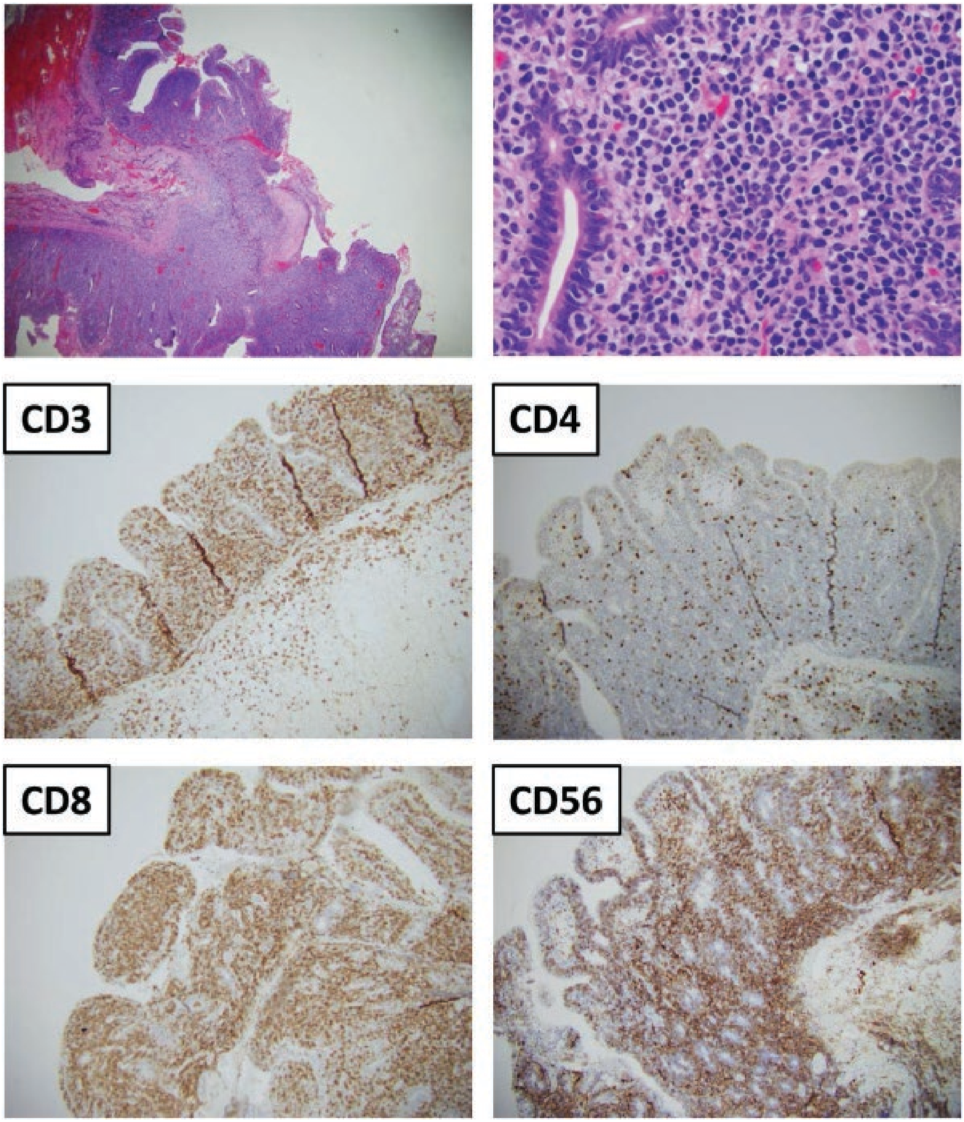

Figure 4 Monomorphic epitheliotropic intestinal T-cell lymphoma. The small intestinal mucosa is diffusely infiltrated by medium-sized atypical lymphoid cells with round nuclei and dispersed chromatin. The villi are markedly distorted. By immunohistochemistry, the atypical lymphoid cells are positive for CD3, CD8, CD56, and TIA-1 (not shown), and negative for CD4 and CD5. The findings are diagnostic for monomorphic epitheliotropic intestinal T-cell lymphoma. The patient also did not have clinical history of celiac sprue.

STAT5B, JAK3, and *SH2B3. SETD2* and *STAT5B* mutations are considered to be specific (Roberti et al. 2016).

Treatment and Prognosis

MEITL has poor clinical outcomes with a median survival of 7 months (Tse et al. 2012). Treatments include surgical resection, combination chemotherapy, and stem cell transplant. Current research suggests that anthracycline-containing chemotherapy combined with surgical resection might be an effective regimen.

Extranodal NK/T Cell Lymphoma, Nasal Type (ENKTL)

ENKTL is predominantly an extranodal lymphoma of NK cell or T cell lineage. Although it most frequently involves the upper aerodigestive tract, especially the nasal cavity, GI tract involvement can also be seen and may be the primary site of presentation. ENKTL is more prevalent in Asians, and natives of Mexico, Central and South America. It is mostly commonly seen in young to middle-aged patients with the median patient age around 44–54. Males are more frequently affected than females (Swerdlow et al. 2017). Patients with GI ENKTL typically present with perforation or GI bleeding. Almost all the ENKTL cases are associated with EBV infection (Swerdlow et al. 2017).

Pathogenesis

The fact that ENKTL is strongly associated with EBV infection indicates the pathogenic role of EBV in this disease. NK/T cells are infected and EBV usually presents in type I/II latency, with only weakly immunogenic EBV antigens LMP1, LMP2, and

EBNA1 expressed (Haverkos et al. 2017). It is proposed that EBV can transform infected cells through constitutive activation of the NF-kB pathway, inhibition of apoptosis, and inducing extensive DNA methylation and genomic instability.

Histopathology

GI tract ENKTL usually shows effacement of the mucosal structure by infiltrates of pleomorphic lymphoma cells. The characteristic angiocentric and angio-destructive pattern is often present. Coagulative necrosis and apoptotic bodies are commonly seen, and mitotic figures are easily found.

The tumor cells are typically positive for CD2, cytoplasmic CD3, CD56, and cytotoxic markers such as Granzyme B, TIA-1, and perforin. They are usually negative for surface CD3 and other common T or NK cell markers including CD4, CD8, CD16, and CD57. In situ hybridization for EBV is positive.

Genetic Abnormalities

Most cases have germline configuration of the *TCR* and *IG* genes, with 10–40% cases show clonal *TCR* gene rearrangement. There is no specific chromosomal translocation associated with ENKTL. The most commonly reported one include del(6)[q21q25] and i(6)(p10). Other frequent chromosomal abnormalities include losses at 1p, 11q, 13q, and 17p, and the gains most commonly at 1q, 2q, 7q, 17q, and 20q (Haverkos et al. 2017). Recurrent mutations were found in tumor suppressor genes (*TP53, DDX3X, and MGA*), members of the *JAK/STAT* cascade (*JAK3* and *STAT3*), and epigenetic modifiers (*KMT2D, BCOR, ARID1A*, and *EP300*) (Jiang et al. 2015).

Treatment and Prognosis

ENKTL involving GI tract is a highly aggressive disease with poor prognosis. It has been reported that patients who were treated with surgery plus chemotherapy had relatively better survival than those treated with chemotherapy alone (Kim et al. 2013). For medically fit patient with localized disease, combined modality therapy (chemotherapy plus radiation therapy) is usually recommended. Several regimens including DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin), Cisplatin followed by VIDL (etoposide, ifosfamide, cisplatin, and dexamethasone), P-GEMOX (pegaspargase, gemcitabine, and oxaliplatin), and modified SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) have been used. Most retrospective data support initiation of radiation first followed by chemotherapy rather than "chemo first" or "sandwich" approaches. For those with advanced disease, an intensive asparaginase-based chemotherapy regimen can provide better outcomes. Anthracycline-based regimens have long known to be ineffective due to probable p-glycoprotein-mediated multidrug resistance. Therefore, most centers use SMILE-, P-GEMOX-, or DDGDP-type chemotherapy for these patients.

EBV titers have a prognostic significance and are often followed longitudinally for disease surveillance. Checkpoint inhibitors have increasingly been incorporated in treatment of relapsed/refractory disease. An allogenic stem cell transplant is considered for patients with relapsed, refractory disease.

NK-cell Enteropathy (NKCE) or Lymphomatoid Gastropathy (LyGa)

In contrast to the aggressive Extranodal NK/T cell lymphoma, NK-cell enteropathy is an indolent disease. Patients usually present with nonspecific GI symptoms. Endoscopy might show lesions such as superficial ulceration, edema, and hemorrhage, involving stomach, small intestine, and colon (Mansoor et al. 2011). The overall pathological and clinical features of NKCE are similar to lymphomatoid gastropathy, another indolent NK-cell LPD identified in the stomachs of Japanese patients (Takeuchi et al. 2010). Therefore, NKCE and LyGa are generally considered to be different manifestations of the same disease process, and they usually present with an indolent disease course.

Pathogenesis

The pathogenesis of NKCE and LyGa are not well understood yet. Possible association between LyGa and *H. pylori* infection has been proposed in some studies but not confirmed yet (Xia et al. 2019)

Histopathology

NKCE is characterized by the expansion of the lamina propria by a relatively well-circumscribed infiltrate of intermediate to large-sized cells with irregular nuclei, small nucleoli, and a moderate amount of pale cytoplasm. Submucosal involvement is rare and epitheliotropism is generally absent. The mucosal glandular architectures are displaced due to the lymphoid infiltrate in the early stages of the disease; and glandular destruction is noted in advanced disease. Notably, in contrast to ENKTL, angio-centricity or angio-destructive pattern of growth is not present in NKCE.

The atypical cells are usually positive for cytoplasmic CD3, CD56, CD7, TIA-1, and/or Granzyme B, but are negative for CD5, CD4, CD8, CD10, CD20, CD30, EBV-latent membrane protein (LMP), PAX-5, CD138, or CD68. Ki-67 staining usually demonstrates a low proliferation index. In situ hybridization for EBV is negative, in contrast to ENKTL.

Genetic Abnormalities

TCR clonality test usually shows absence of TCR-gamma (γ) gene rearrangement. Recurrent *JAK3* mutation has been reported in some NK-cell enteropathy cases (Xiao et al. 2019)

Treatment and Prognosis

NKCE and LyGa have an indolent disease course. In patients who were followed without treatment, none developed progressive disease or died of lymphoma (Mansoor et al. 2011; Xia et al. 2019).

Indolent T Cell Lymphoproliferative Disorder (ITLPD) of the Gastrointestinal Tract

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract is a rare clonal T-cell lymphoproliferative disorder. It is included as a provisional entity in the current 2016 World Health Organization classification (Swerdlow et al. 2017). The disease most frequently affects the small bowel and colon, although all sites of the GI tract could be involved. Patients usually present with nonspecific GI symptoms in adulthood, with male being affected more than female. Majority of patients have an indolent clinical course with persistent disease.

Pathogenesis

No specific etiology has been identified for ITLPD yet, although few cases are reported in patients with history of inflammatory bowel disease and autoimmune disorders (Matnani et al. 2017; Perry et al. 2013). Recent study suggested that the genetic alterations of the *JAK-STAT* pathway might play a role in the pathogenesis of ITLPD of the GI tract (Soderquist et al. 2020).

Histopathology

ITLPD of the GI tract shows a dense diffuse or nodular infiltrate of small-sized lymphocytes in the lamina propria. Focal infiltration of the muscularis mucosae and submucosa might be present. Epitheliotropism is rarely seen. The atypical cells are usually monotonous small lymphocytes with round, ovoid or mildly irregular nuclei, and scant or moderate cytoplasm. There is no angio-centricity, angio-destruction, ulceration, or necrosis.

The lymphoid cells express T cell markers such as CD2, CD3, and CD5. Most cases are CD8-positive/CD4-negative, but CD4-positive/CD8-negative cases have also been reported (Matnani et al. 2017). All the reported cases expressed surface T-cell receptor (TCR) αβ. The Ki-67 proliferation index is usually low.

Genetic Abnormalities

Nearly all the cases show clonal TCR β or γ gene rearrangement. Next-generation sequencing have revealed genetic alterations in around 80% of the cases, including mutations in *JAK-STAT* signaling pathway genes (*STAT3, SOCS1*), epigenetic modifier genes (*TET2, DNMT3A, KMT2D*), and structural alteration of the *IL2* gene (Soderquist et al. 2020).

Treatment and Prognosis

Patients usually have a chronic relapsing clinical course with prolonged survival despite poor response to conventional chemotherapy.

Key Take Home Messages

- The biology and molecular pathogenesis of GI lymphomas has been better characterized and is leading to personalized treatment strategies.
- Management algorithms for lymphomas are evolving and several new targeted, immunologic, and cellular therapies have been approved and several others being explored in clinical trials.
- MALT lymphomas remain one of the lymphomas that when associated with H pylori can be effectively treated with only antibiotic therapy.
- Engineered cellular therapy in the form of CAR T-cell therapy is now approved for relapsed and refractory DLBCL, FL and MCL.
- Targeted agents like BTK inhibitors, immunomodulatory drugs (IMiDs), PI-3 kinase and EZH2 inhibitors are very effective in relapsed indolent B-cell lymphomas like MZL and FL.

Knowledge Gaps

- Resistance mechanisms to upfront chemoimmunotherapy remain poorly characterized.
- Translational research is needed to advance precision medicine for newly characterized molecular subclasses of lymphomas.
- The optimal sequence of newer treatment strategies for lymphomas especially CAR-T needs to be better characterized.
- Aggressive T-cell lymphomas affecting the GI tract like EATL and MEITL are still associated with a very guarded prognosis especially in relapsed settings. Relapsed T-cell lymphomas remain an area of unmet clinical need for identifying newer molecular targets and developing effective therapeutics.

Areas for Further Research

Optimization of targeted therapy for each lymphoma type
Earlier diagnosis of lymphomas by non-invasive testing

Trusted Websites for Further Reading

https://lymphoma.org
https://www.cancer.org/cancer/lymphoma.html

References

Alizadeh, A.A., Eisen, M.B., Davis, R.E. et al. (2000). Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 403 (6769): 503–511.

Al-Saleem, T. and Al-Mondhiry, H. (2005). Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. *Blood* 105 (6): 2274–2280.

Barrans, S., Crouch, S., Smith A. et al. (2010). Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. *J Clin Oncol* 28 (20): 3360–3365.

Bautista-Quach, M.A., Ake, C.D., Chen, M. and Wang, J.. (2012). Gastrointestinal lymphomas: morphology, immunophenotype and molecular features. *J Gastrointest Oncol* 3 (3): 209–225.

Chan, J.K.C., Chan, A.C.L., Cheuk, W. et al. (2011). Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent γδ T-cell receptor expression. *Am J Surg Pathol* 35 (10): 1557–1569.

Chander, U., Leeman-Neill, R.J., and Bhagat, G. (2018). Pathogenesis of enteropathy-associated T cell lymphoma. *Curr Hematol Malig Rep* 13 (4): 308–317.

Chen, L.-T., Lin, J.-T., Shyu, R.-Y. et al. (2001). Prospective study of Helicobacter pylori eradication therapy in stage IE high-grade mucosa-associated lymphoid tissue lymphoma of the stomach. *J Clin Oncol* 19 (22): 4245–4251.

Delabie, J., Holte, H., Vose, J.M. et al. (2011). Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. *Blood* 118 (1): 148–155.

Deleeuw, R.J., Zettl, A., Klinker, E. et al. (2007). Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. *Gastroenterology* 132 (5): 1902–1911.

Dojcinov, S.D., Venkataraman, G., Raffeld, M. et al. (2010). EBV positive mucocutaneous ulcer–a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol* 34 (3): 405.

England, R.J., Pillay, K., Davidson, A. et al. (2012). Intussusception as a presenting feature of Burkitt lymphoma: implications for management and outcome. *Pediatr Surg Int* 28 (3): 267–270.

Ferreri, A.J. and Montalbán, C. (2007). Primary diffuse large B-cell lymphoma of the stomach. *Crit Rev Oncol Hematol* 63 (1): 65–71.

Freeman, C., Berg, J.W., and Cutler, S.J. (1972). Occurrence and prognosis of extranodal lymphomas. *Cancer* 29 (1): 252–260.

Ghimire, P., Wu, G.-Y., and Zhu, L. (2011). Primary gastrointestinal lymphoma. *World J Gastroenterol: WJG* 17 (6): 697.

Hans, C.P., Weisenburger, D.D., Greiner, T.C. et al. (2004). Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 103 (1): 275–282.

Haverkos, B.M., Coleman, C., Gru, A.A. et al. (2017). Emerging insights on the pathogenesis and treatment of extranodal NK/T cell lymphomas (ENKTL). *Discov Med* 23 (126): 189–199.

Hayashi, H., Onishi, Y., Mitsuoka, H. et al. (2013). Regression of follicular lymphoma of the duodenum following eradication of H. pylori infection. *Int Med* 52 (23): 2611–2614.

Hong, Y.S., Woo, Y.S., Park, G. et al. (2016). Endoscopic findings of enteropathy-associated T-cell lymphoma type II: a case series. *Gut Liver* 10 (1): 147.

Hussell, T., Isaacson, P.G., Spencer, J. and Crabtree, J.E. (1993). The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. *Lancet* 342 (8871): 571–574.

Inagaki, H., Nakamura, T., Li, C. et al. (2004). Gastric MALT lymphomas are divided into three groups based on responsiveness to helicobacter pylori eradication and detection of API2-MALT1 fusion. *Am J Surg Pathol* 28 (12): 1560–1567.

Ioannidis, O., Cheva, A., Kakoutis, E. et al. (2011). Acute adult intussusception caused by primary cecal non Hodgkin lymphoma. *Acta Gastro-Enterol Belg* 74 (3): 451–453.

Iwamuro, M., Kondo, E., Takata, K. et al. (2016). Diagnosis of follicular lymphoma of the gastrointestinal tract: a better initial diagnostic workup. *WJG, World J Gastroenterol* 22 (4): 1674–1683.

Jaso, J., Chen, L., Li, S. et al. (2012). CD5-positive mucosa-associated lymphoid tissue (MALT) lymphoma: a clinicopathologic study of 14 cases. *Human Pathol* 43 (9): 1436–1443.

Jiang, L., Gu, Z.-H., Yan, Z.-X. et al. (2015). Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. *Nat Genet* 47 (9): 1061–1066.

Kim, S.J., Jung, H.A., Chuang, S.-S. et al. (2013). Extranodal natural killer/T-cell lymphoma involving the gastrointestinal tract: analysis of clinical features and outcomes from the Asia Lymphoma study group. *J Hematol Oncol* 6 (1): 86.

Kramer, M.H.H., Hermans, J., Wijburg, E. et al. (1998). *Clinical relevance of BCL2, BCL6, and MYC rearrangements in diffuse large B-cell lymphoma. Blood. J Am Soc Hematol* 92 (9): 3152–3162.

Kuo, S.H., Yeh, K.H., Chen, L.T. et al. (2014). Helicobacter pylori-related diffuse large B-cell lymphoma of the stomach: a distinct entity with lower aggressiveness and higher chemosensitivity. *Blood Cancer J* 4 (6): e220–e220.

Lecuit, M., Abachin, E., Martin, A. et al. (2004). Immunoproliferative small intestinal disease associated with campylobacter jejuni. *N Engl J Med* 350 (3): 239–248.

Lewis, R.B., Mehrotra, A.K., Rodríguez, P. et al. (2014). From the radiologic pathology archives: gastrointestinal lymphoma: radiologic and pathologic findings. *Radiographics* 34 (7): 1934–1953.

Li, J.-Y., Gaillard, F., Moreau, A. et al. (1999). Detection of translocation t (11; 14)(q13; q32) in mantle cell lymphoma by fluorescence in situ hybridization. *Am J Pathol* 154 (5): 1449–1452.

Mansoor, A., Pittaluga, S., Beck, P.L. et al. (2011). NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. *Blood J Am Soc Hematol* 117 (5): 1447–1452.

Matnani, R., Ganapathi, K.A., Lewis, S.K. et al. (2017). Indolent T-and NK-cell lymphoproliferative disorders of the gastrointestinal tract: a review and update. *Hematol Oncol* 35 (1): 3–16.

Mention, -J.-J., Ahmed, M.B., Bègue, B. et al. (2003). Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. *Gastroenterology* 125 (3): 730–745.

Morgner, A., Miehlke, S., Fischbach, W. et al. (2001). Complete remission of primary high-grade B-cell gastric lymphoma after cure of Helicobacter pylori infection. *J Clin Oncol* 19 (7): 2041–2048.

Mori, M., Kobayashi, Y., Maeshima, A.M. et al. (2010). The indolent course and high incidence of t (14; 18) in primary duodenal follicular lymphoma. *Ann Oncol* 21 (7): 1500–1505.

Nicolae, A., Xi, L., Pham T.H. et al. (2016). Mutations in the JAK/STAT and RAS signaling pathways are common in intestinal T-cell lymphomas. *Leukemia* 30 (11): 2245–2247.

Obermann, E.C., Diss, T.C., Hamoudi, R.A. et al. (2004). Loss of heterozygosity at chromosome 9p21 is a frequent finding in enteropathy-type T-cell lymphoma. *J Pathol: J Pathol Soc Great Britain Ireland* 202 (2): 252–262.

Offit, K., Coco, F.L., Louie, D.C. et al. (1994). Rearrangement of the bcl-6 gene as a prognostic marker in diffuse large-cell lymphoma. *N Engl J Med* 331 (2): 74–80.

Pérez-Galán, P., Dreyling, M., and Wiestner, A. (2011). Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood* 117 (1): 26–38.

Perry, A.M., Warnke, R.A., Hu, Q. et al. (2013). Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. *Blood J Am Soc Hematol* 122 (22): 3599–3606.

Psyrri, A., Papageorgiou, S., and Economopoulos, T. (2008). Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pitfalls and management. *Ann Oncol* 19 (12): 1992–1999.

Roberti, A., Dobay, M.P., Bisig, B. et al. (2016). Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. *Nat Commun* 7 (1): 1–13.

Rohatiner, A., d'Amore, F., Coiffier, B. et al. (1994). Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol* 5 (5): 397–400.

Romaguera, J.E., Medeiros, L.J., Hagemeister, F.B. et al. (2003). Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer Interdisciplinary Int J Am Cancer Soc* 97 (3): 586–591.

Rosenwald, A., Wright, G., Chan, W.C. et al. (2002). The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med* 346 (25): 1937–1947.

Ruskoné-Fourmestraux, A. and Audouin, J. (2010). Primary gastrointestinal tract mantle cell lymphoma as multiple lymphomatous polyposis. *Best Pract Res Clin Gastroenterol* 24 (1): 35–42.

Sagaert, X., Van Cutsem, E., De Hertogh, G. et al. (2010). Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. *Nat Rev Gastroenterol Hepatol* 7 (6): 336–346.

Salar, A., Juanpere, N., Bellosillo, B. et al. (2006). Gastrointestinal involvement in mantle cell lymphoma: a prospective clinic, endoscopic, and pathologic study. *Am J Surg Pathol* 30 (10): 1274–1280.

Salaverria, I., Royo, C., Carvajal-Cuenca, A. et al. (2013). CCND2 rearrangements are the most frequent genetic events in cyclin D1– mantle cell lymphoma. *Blood* 121 (8): 1394–1402.

Schmatz, A.-I., Streubel, B., Kretschmer-Chott, E. et al. (2011). Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. *J Clin Oncol* 29 (11): 1445–1451.

Shia, J., Teruya-Feldstein, J., Pan, D. et al. (2002). Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. (0147-5185 (Print)).

Sieniawski, M., Angamuthu, N., Boyd, K. et al. (2010). Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. *Blood* 115 (18): 3664–3670.

Soderquist, C.R., Patel, N., Murty, V.V. et al. (2020). Genetic and phenotypic characterization of indolent T-cell lymphoproliferative disorders of the gastrointestinal tract. *haematologica* 105 (7): 1895.

Stolte, M., Bayerdörffer, E., Morgner, A. et al. (2002). Helicobacter and gastric MALT lymphoma. *Gut* 50 (Suppl 3): III19–III24.

Swerdlow, S.H., Campo, E., Harris, N.L. et al. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 127 (20): 2375–2390.

Swerdlow, S.H., Campo, E., Harris, N.L. et al. (2017). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, Revised 4e. IARC.

Swinson, C.M., Coles, E.C., Slavin, G. and Booth, C.C. (1983). Coeliac disease and malignancy. *Lancet* 321 (8316): 111–115.

Takeuchi, K., Yokoyama, M., Ishizawa, S. et al. (2010). Lymphomatoid gastropathy: a distinct clinicopathologic entity of self-limited pseudomalignant NK-cell proliferation. *Blood J Am Soc Hematol* 116 (25): 5631–5637.

Thomas, J.A., Allday, M.J., and Crawford, D.H. (1991). Epstein-Barr virus-associated lymphoproliferative disorders in immunocompromised individuals. *Adv Cancer Res* 57: 329–380.

Toyoda, H., Yamaguchi, M., Nakamura, S. et al. (2001). Regression of primary lymphoma of the ampulla of Vater after eradication of Helicobacter pylori. (0016-5107 (Print)).

Troppan, K., Wenzl, K., Neumeister, P. and Deutsch, A. (2015). Molecular pathogenesis of MALT lymphoma. *Gastroenterol Res Pract* 2015: 102656–102656.

Tse, E., Gill, H., Loong, F. et al. (2012). Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia Lymphoma Study Group. *Am J Hematol* 87 (7): 663–668.

Violeta Filip, P., Cuciureanu, D., Diaconu, L.S. et al. (2018). MALT lymphoma: epidemiology, clinical diagnosis and treatment. *J Med Life* 11 (3): 187–193.

Wotherspoon, A.C., Diss, T.C., Pan, L. et al. (1993). Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet* 342 (8871): 575–577.

Xia, D., Morgan, E.A., Berger, D. et al. (2019). NK-cell enteropathy and similar indolent lymphoproliferative disorders: a case series with literature review. *Am J Clin Pathol* 151 (1): 75–85.

Xiao, W., Gupta, G.K., Yao, J. et al. (2019). Recurrent somatic JAK3 mutations in NK-cell enteropathy. *Blood* 134 (12): 986–991.

Yaguchi, T., Imaeda, H., Kizaki, M. et al. (2010). Partial regression of duodenal lesions of intestinal follicular lymphoma after antibiotic treatment. *Dig Endosc* 22 (4): 316–318.

27 Palliative and Supportive Medicine in Gastrointestinal Oncology

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[Aspects of Palliative care are also discussed in Chapter 28].

Introduction to Palliative/Supportive Medicine

Palliative Medicine, now sometimes referred to as *supportive* medicine, is specialized medical care for seriously ill patients and their families. Palliative medicine strives to provide an additional "layer of support" to patients and families with a focus on improved quality of life at all stages of illness from time of diagnosis through end of life (Palliative Care Definition). Contrary to widespread belief, the provision of palliative medicine is not limited to the care of patients imminently approaching the end of life and can be provided in parallel with curative treatment (Palliative Care Definition). Hospice care, specifically, is limited to patients in the final stages of life and in the United States the hospice care benefit is limited to patients with a prognosis of six months or less and in whom curative treatments are no longer being pursued.

Initially rooted in oncology, the field of palliative medicine has experienced tremendous expansion since the 1960s. The modern-day hospice movement stems largely from the work of Dame Cicely Saunders, a nurse who founded St. Christopher's Hospice in London, UK in 1967. Saunders' work emphasized the concept of "total pain" in the care of the dying – suggesting that distress at end of life is multifaceted involving the interrelated elements of mind, body, and spirit (Brooksbank 2009; Clark 2007).

Saunders' work focused largely on patients with advanced, incurable malignancies often experiencing high symptom burdens requiring aggressive alleviation of distress. Since then, the field of palliative medicine has transcended oncologic boundaries and come to include the care of patients with life-altering and life-limiting nonmalignant diseases as well (Clark 2007). While the initial work of Saunders and colleagues focused primarily on imminently dying patients, leaders in palliative medicine over the past two decades have stressed the benefits of early palliative medicine intervention. In 2002, the World Health Organization (WHO) recommended palliative medicine treatment alongside disease directed oncologic treatments (Brooksbank 2009). Additionally, in 2012, the American Society of Clinical Oncologists (ASCO) released a panel consensus recommending the routine involvement of palliative medicine in oncology practice even in the initial stages of malignancy (Smith et al. 2012).

Palliative medicine involves an interdisciplinary approach to the care and management of patients with serious illness. Interdisciplinary teams may involve physicians, advanced practice providers, nurses, chaplains, social workers, and pharmacists each with their own unique skill set to address the complexities of improving quality of life for seriously ill patients and their families. Symptoms vary according to illness. In gastrointestinal malignancies, common physical symptoms include pain, nausea/vomiting, anorexia, and constipation all of which should be aggressively treated with the goal of decreased symptom burden, improved tolerance of disease directed treatments, and better overall quality of life.

Pain

Pain related to malignancy is one of the most common and distressing symptoms that patients with cancer may experience. The prevalence of cancer-related pain is almost 40% after curative treatment, 55% during cancer treatment, and over 66% in patients with metastatic disease (van den Beuken-van Everdingen et al. 2016). Despite this, the widespread availability of and access to medications to treat pain are limited (Berterame et al. 2016). Further, cancer-related pain is undertreated in over 40% of patients (Apolone et al. 2009; Deandrea et al. 2008). This is particularly notable in this patient population, as inadequately treated pain is associated with decreased quality of life, manifesting through increased rates of depression, anxiety, posttraumatic stress disorder, insomnia, and functional impairment (Goldstein and Morrison 2013).

The main classifications for pain include nociceptive and neuropathic. Nociceptive pain is further subdivided into

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visceral pain and somatic pain. Visceral pain (dull, diffuse) relates to insults or injury of internal organs, such as the liver. Somatic pain (sharp, well-localized) refers to injury of skin and deep tissue (Goldstein and Morrison 2013). Neuropathic pain is caused by damage to the somatosensory nervous system leading to inappropriate neural excitability. This type of pain is often described as burning, numb, pins-needles, electric-type, or shooting.

Given its subjective nature, pain is best assessed by patient report. In order to tailor treatment appropriately, comprehensive interview is essential, assessing the following pain elements: onset, location, duration, character or quality, alleviating and aggravating factors, radiation, timing, and severity.

There are many pharmacotherapeutic tools that can be utilized in the management of cancer-related pain, shown in Table 1.

While it is beneficial to treat pain with multiple agents that have varying mechanisms of action, opioids remain a mainstay for the management of moderate to severe cancer-related pain (Wiffen et al. 2017). Starting doses of opioids will depend on several factors: previous recent opioid use, age, renal function, and liver function. It is also helpful to determine what opioids have worked in the past if a patient has previously been on opioids. When initiating opioids, it is most appropriate to start with short-acting opioids on an as-needed basis. The duration of action for these medications is ~4 hours. Worldwide, morphine is the most widely available and cost-effective opioid. The starting dose of morphine is 0.05–0.1 mg/kg. Starting doses of opioids can be found in Table 2.

Short-acting opioids should be titrated based on the analgesia produced and adverse effects encountered. The peak effect for parenteral opioids occurs at 10–15 minutes; this effect occurs at 60–90 minutes for enteral opioids. If the patient continues to have intolerable pain after the peak effect of the short-acting opioid has been reached, giving additional doses is warranted. For mild intolerable pain, clinicians may increase the dose by 25%. For moderate and severe intolerable pain, the dose may be increased by 50% and 100%, respectively. Table 3 shows opioid analgesic equivalents.

Table 1 Medication classes for cancer-related pain.

Opioids
Acetaminophen
Nonsteroidal anti-inflammatories
Steroids
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)
Tricyclic Antidepressants (TCA)
Gabapentinoids
NMDA-antagonists (e.g., ketamine)
Sodium channel blockers (e.g., lidocaine)

Table 2 Starting doses for short-acting opioids.

	Intravenous/subcutaneous	Oral
Morphine*	3–7 mg	10–20 mg
Hydromorphone	0.4–1 mg	2–4 mg
Oxycodone	–	7.5–10 mg
Hydrocodone	–	10–20 mg

*This table provides starting doses of opioids for a 70 kg patient using a starting morphine dose of 0.05–0.1 mg/kg.

Table 3 Opioid analgesic equivalents.

Opioid agonist	Intravenous/subcutaneous (mg)	Oral (mg)
Morphine	10	30
Hydrocodone	–	30
Oxycodone	–	20
Hydromorphone	1.5	7.5

The addition of long-acting opioids is appropriate when the patient is on chronic opioids for cancer-related pain, defined as more than two weeks of therapy. Additionally, cancer pain should be expected to persist in the future if long-acting agents are to be considered. For patients on chronic opioids, clinicians should calculate the daily opioid needs in oral morphine equivalents (OME) in order to track opioid use over time. Long-acting opioids are helpful for maintaining baseline pain control, decreasing as-needed medication use, and maintaining analgesia during sleep time. When pain is adequately managed and OME use is stable, a long-acting agent may be started or titrated. The long-acting agent should ultimately account for 2/3–¾ of a patient's total daily OME. This will help to ensure that the patient will not require frequent as needed short-acting medications. Please see Table 4 for available long-acting formulations.

Opioids should be used in conjunction with other medication classes to treat pain in a multimodal fashion and decrease the potential for adverse effects. The most common adverse effect is constipation (see below). Other adverse effects include nausea, vomiting, sedation, pruritus, and – rarely – respiratory depression (Goldstein and Morrison 2013).

Neuropathic pain is common in patients with cancer. This can occur as a result of chemotherapy (see below) or due to direct nerve injury by cancerous lesions. Opioids are effective for the management of neuropathic pain. In addition, several agents can be administered either alone or in conjunction with opioids. Neuropathic agents include SNRIs, TCAs, and gabapentinoids (Aiyer et al. 2018). Please see Table 5 for specific agents. For dosing guidelines, please see section on psychiatric symptoms below. Multiple trials have shown that the combination of neuropathic agents with opioids results in

Table 4 Long-acting opioid formulations and considerations (McPherson 2018; Nicholson 2009; Van Nimmen et al. 2010; Yenikomshian et al. 2017).

Extended- release opioid agonists	Considerations
Morphine	Inexpensive; caution in renal disease
Oxycodone	Moderate expense
Hydromorphone	Cost-prohibitive; not widely available
Hydrocodone	Cost-prohibitive; not widely available
Methadone	Complex medication with widely varying half-life; additional mechanism of action via NMDA antagonism; consult with palliative care or pain specialist prior to use
Fentanyl transdermal	Particularly useful in patients unable to take oral medications; absorption in frail patients with low muscle mass may be altered; some patients feel stigma with wearing medication patches; ratio of transdermal fentanyl to OME is 1:2 (e.g., a fentanyl patch dose of 25 mcg/hr delivers 50 mg OME in a 24-hour period)

Table 5 Non-opioid agents for neuropathic pain.

Gabapentinoids
Gabapentin
Pregabalin
SNRIs
Duloxetine
Venlafaxine
TCAs
Desipramine
Nortriptyline

greater analgesia than either agent class alone (Gilron et al. 2005, 2015). Also, various studies endorse combined use of SNRIs or TCAs with gabapentinoids, as the combination produces greater analgesia without dramatic increases in adverse effects (Gilron et al. 2009; Matsuoka et al. 2019). In addition to alleviating pain, these non-opioid options may also be helpful for treating concomitant mood disorders, which are prevalent in this patient population. Therefore, it can prove advantageous to treat multiple symptoms/syndromes with fewer medications.

Chemotherapy-induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) or chemotherapy-induced neuropathy (CIN) has become one of the most troublesome and dose-limiting toxicities for GI cancer patients (Loprinzi et al. 2020). It affects up to 30–60% of patients (Seretny et al. 2014), usually manifest as distal extremity pain, tingling, and numbness. It always affects the longest nerves first, so the fingertips and toes are the first to manifest symptoms. Besides limiting the doses and schedule of treatment, potentially compromising results, patients with persistent CIN have a 1.6-fold risk of serious falls. The damage to the nerves depends on the agents used, but is common with oxaliplatin and the taxanes (paclitaxel, docetaxel) that form the backbone of many GI-cancer treatment regimens. The pain is explainable by damage to the usual pain fibers. The numbness and tingling are less well described but is due to damage signals coming from the injured heat, cold, itch, touch, and other fibers.

At present, there is no known way of preventing CIN, although trials are in progress of several promising agents. An effective agent should not cause harm and should protect the nerves but not the cancer. An agent that protects against diabetic neuropathy, oral alpha-lipoic acid, actually worsened CIN, almost certainly due to a different mechanism of toxic damage to the nerves (Guo et al. 2014). This harm persisted for at least two years (Hershman et al. 2018). Cooling the extremities (cryotherapy) appeared promising in one small Japanese trial (Hanai et al. 2017), but had no effect (Ruddy et al. 2019) and was poorly tolerated (Griffiths et al. 2018) in two larger United States trials. Compression therapy to reduce blood flow to the extremities was similarly unsuccessful (Kanbayashi et al. 2020) and cannot be recommended at this time.

The American Society of Clinical Oncology practice guideline states that duloxetine is the only drug known to effectively treat the pain of CIN in a randomized trial, and that commonly used drugs like gabapentin and pregabalin were no more effective than placebo (Loprinzi et al. 2020). Duloxetine reduced pain scores by 0.6 to 1.0 point on a 10-point scale, about a 10% reduction, but had no sustained effect on the numbness and tingling sensations (Smith et al. 2013). No other drug has been proven effective in a randomized controlled trial. In a nonrandomized trial, 1–2% topical menthol reduced the areas of hypersensitivity, and 82% of patients reported an improvement in their Brief Pain Inventory score, with no toxicity (Fallon et al. 2015). In our own practice, the combination of nortriptyline and gabapentin where both are escalated together, can be effective (Gilron et al. 2005). Controlled release oxycodone given before starting oxaliplatin chemotherapy doubled the number of cycles and total dosage of oxaliplatin, compared to no treatment, and the number who continued until progressive disease was 62% with oxycodone versus 20% without (stoppage due to CIN). However, only 34% of oxycodone patients were able to stop the oxycodone after oxaliplatin treatment, suggesting a long-term commitment to opioid treatment (Nagashima et al. 2014). One promising procedure is Scrambler Therapy, a form of superficial neuromodulation, that reduced pain, numbness, and tingling compared to transcutaneous electrical nerve stimulation, but confirmatory trials are needed (Loprinzi et al. 2020). Similarly, auricular (ear) acupressure reduced pain, numbness, tingling, and stiffness by 54% in a small trial (Yeh et al. 2019), with no toxicity and dramatic reductions in serum inflammatory proteins and improvements in quantitative neurosensory testing (Yeh et al. 2019), but randomized trials are needed.

Constipation

Constipation is a bothersome and frequently encountered symptom in cancer patients. It has been estimated that the prevalence of constipation in palliative care patients with cancer is anywhere between 23% and 65% (Larkin et al. 2008). A prospective study involving patients with advanced cancer admitted to a Taiwanese palliative care unit found that constipation was the third most common and severe symptom, affecting 63.5% of admitted patients (Tai et al. 2016). Notably, patients with gastrointestinal malignancies were disproportionately affected by constipation and other gastrointestinal symptoms (Tai et al. 2016).

Constipation adversely affects quality of life in the palliative medicine population (Ginex et al. 2020; Hasson et al. 2020; Larkin et al. 2008, 2018; Muldrew et al. 2018). In addition to its physical effects on the body, constipation can also generate social and psychological suffering (Hasson et al. 2020; Moschen et al. 2022; Muldrew et al. 2018). Despite this, constipation is thought to be under-recognized and inadequately treated in cancer patients (Alvaro et al. 2022; Hasson et al. 2020; Muldrew et al. 2018). Qualitative research suggests that physicians often view constipation through a purely physical lens and fail to recognize its broader impact on quality of life and overall importance. Additionally, "embarrassment" has been identified as an impediment to recognition and patients have reported preferences for healthcare providers to more openly discuss and assess constipation during visits (Hasson et al. 2020).

Definition and Assessment

Further complicating its recognition and assessment in cancer patients, there is no universally accepted definition of constipation (Alvaro et al. 2022; Davies et al. 2020; Dzierżanowski and Larkin 2020; Muldrew et al. 2018). The Rome IV criteria (Rome IV Criteria 2022) provides a general approach to the diagnosis of functional constipation and opioid-induced constipation. However, arguments have been made that these criteria are too restrictive for the diagnosis of constipation in the palliative care population leading to underdiagnosis (Dzierżanowski and Larkin 2020). In our clinical practice, we have a low threshold to suspect constipation in patients with gastrointestinal cancers, especially those using opioids and other traditionally constipating medications. A number of patient assessment tools have been used to assist in the formal diagnosis of constipation as outlined in Table 1. Of these, expert consensus suggests that the bowel function index (BFI) is the most clinically practical given its brevity and simplicity (Larkin et al. 2018).

Constipation assessment tools (Adapted from Larkin et al. 2018)
PAC-SYM (Patient Assessment Constipation-Symptoms)
PAC-QOL (Patient Assessment Constipation-Quality of Life)
CAS (Constipation Assessment Scale)
BFI (Bowel Function Index)
SSS (Stool Symptom Screener)
BSFS (Bristol Stool Form Scale)
VPS (Victoria Bowel Performance Scale)
BFD (Bowel Function Diary)

Expert consensus by the Multinational Association for Supportive Care in Cancer (MASCC) recommends the following items be addressed when assessing for constipation in patients with advanced cancer (Davies et al. 2020):

1. Frequency of bowel movements?
2. Presence of straining?
3. Consistency of bowel movements?
4. Sensation of incomplete evacuation?
5. Sensation of obstruction in rectum or anus?
6. Current or prior use of laxatives and or other remedies for constipation?
7. Changes in bowel function since starting opioid therapy?

Additionally, the use of a visual aid to best assess the consistency of stools such as the widely used Bristol Stool Form Scale may be beneficial (Davies et al. 2020). Physical exam including a comprehensive abdominal exam and digital rectal examination (especially if fecal impaction suspected) can aid in the diagnosis, help determine the etiology of constipation, and also assess for sequelae of untreated constipation (e.g. fissures, hemorrhoids) (Davies et al. 2020).

Etiology

In addressing constipation, identifying the etiology can help inform treatment (Davies et al. 2020; Larkin et al. 2018; LeFebvre et al. 2020). Given the complexity of cancer and cancer treatments, the cause of constipation in gastrointestinal malignancy is often multifactorial. Structurally speaking, tumor and inflammation of the gastrointestinal tract and abdominal compartment as well as surgical procedures related to disease treatment can increase the risk of constipation and even bowel obstruction (Moschen et al. 2022). As cancer progresses, poor oral intake, pain, dehydration, and immobility may further worsen constipation (Larkin et al. 2018; LeFebvre et al. 2020; Moschen et al. 2022). Additionally, many chemotherapeutic agents can instigate constipation (e.g. vinka alkaloids, hormonal agents, thalidomide, and platinum-based agents) (Gibson and Keefe 2006; Larkin et al. 2018; LeFebvre et al. 2020; Moschen et al. 2022). Table 2 lists additional medications commonly used in patients with GI cancers that have been associated with constipation.

Common medications associated with constipation (Larkin et al. 2018; Moschen et al. 2022)

- Anticholinergics
- Antiemetics (5-HT3 receptor antagonists)
- Antihistamines
- Calcium channel blockers
- Diuretics
- Iron supplements
- Opioids
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants

Opioid-induced constipation is especially common in patients with cancer. It has been estimated that 47–94% of patients using opioids for cancer-related pain experience opioid-induced constipation (Alvaro et al. 2022). The role of opioids in constipation involves their blockade of mu receptors in submucosal and myenteric plexus neurons of the GI tract leading to reduced excitability of neurons and decreased neurotransmitter release resulting in less gastrointestinal motility and secretion (Alvaro et al. 2022; De Giorgio et al. 2021). It is important that bowel patterns be assessed both before and after initiation of opioid therapy and regularly evaluated to monitor for changes (Alvaro et al. 2022). Unlike other effects of opioids, patients typically do not develop tolerance with regards to constipation (Davies et al. 2020).

Treatment

Inadequately managed constipation can lead to persistent discomfort and development of complications including but not limited to fecal impaction, bowel obstruction, hemorrhoids, rectal fissures and intestinal perforation (Moschen et al. 2022). We recommend routine assessment for constipation throughout a patient's cancer trajectory. All cancer patients should receive counseling on lifestyle modification to prevent constipation including advice on fluid intake, physical activity, and dietary modification (e.g., fiber intake) (LeFebvre et al. 2020). Additionally, patients should be prescribed a laxative at the time of opioid initiation to aid in the prevention of opioid-induced constipation specifically (Alvaro et al. 2022; Boland and Boland 2017; LeFebvre et al. 2020).

Often, patients are unable to realistically modify their lifestyles due to the advanced nature of their malignancy and resulting debility and cachexia. Additionally, lifestyle modification such as increased fiber intake may have minimal effectiveness in opioid-induced constipation (De Giorgio et al. 2021). First-line pharmacologic treatment for constipation should include an oral osmotic or stimulant laxative (Larkin et al. 2018). These can be combined to achieve the desired effect. There is minimal data to recommend one type of laxative over another (Davies et al. 2020; Larkin et al. 2018). Treatment should be patient centered with consideration of side effects and patient ability to tolerate the prescribed laxative medication (Davies et al. 2020). Current evidence does not support the use of stool softeners such as docusate either alone or in combination with stimulant laxatives in the treatment of constipation although the use of stool softeners remains common in clinical practice (*Dioctyl Sulfosuccinate or Docusate (Calcium or Sodium) for the Prevention or Management of Constipation: A Review of the Clinical Effectiveness* 2014; Hawley and Byeon 2008). Table 6 lists commonly prescribed laxatives by drug class.

For patients with constipation refractory to oral stimulant or osmotic laxatives, additional options include rectal delivery of medications in the form of suppositories and or enemas (Larkin et al. 2018). Manual disimpaction may be necessary in some patients (De Giorgio et al. 2021; Larkin et al. 2018). Enemas should be used cautiously especially in patients with bowel obstruction, colitis, diverticulosis, neutropenia/thrombocytopenia, and those with a history of pelvic radiation to avoid further complications (De Giorgio et al. 2021). Enemas and suppositories can be helpful especially when there is a large burden of stool in the rectum or fecal impaction although patients may have negative perceptions regarding their use (Larkin et al. 2018).

Patients with opioid-induced constipation that has been refractory to traditional laxative therapy may benefit from the use of a peripherally acting mu opioid receptor antagonists (PAMORAs) such as naloxegol, naldemedine, and methylnaltrexone (subcutaneous option available) (Alvaro et al. 2022; Boland and Boland 2017; Candy et al. 2018; Davies et al. 2020; De Giorgio et al. 2021; Hanson et al. 2019; Larkin et al. 2018; LeFebvre et al. 2020). The availability of these agents varies internationally and use is often limited by expense. One US study found that approximately three quarters of hospice agencies surveyed were not using these agents in their management of constipation (Sera and McPherson 2018). Additional specialist medications such as lubiprostone, prucalopride, and linaclotide can be considered

Table 6 Commonly prescribed laxatives (Adapted from Hanson et al. 2019).

Osmotic laxatives	Polyethylene glycol Magnesium citrate Lactulose
Stimulant laxatives	Senna Bisacodyl (oral and suppository) Sodium picosulfate
Stool softeners	Docusate sodium
PAMORAs	Naldemedine (oral) Naloxegol (oral) Methylnaltrexone (oral or subcutaneous)

although evidence to support their use is mixed and research regarding their safety and efficacy is ongoing (Ginex et al. 2020; Hanson et al. 2019; Hisanaga et al. 2019; LeFebvre et al. 2020).

For patients at end of life, we recommend the continued treatment of constipation until burden on patients and caregivers outweighs benefit. For patients imminently approaching end of life and in whom oral medications are no longer feasibly an option, suppositories (e.g., bisacodyl) are available. There is no definitive recommendation as to when to stop pharmacologic treatment of constipation at end of life (Muldrew et al. 2018) and it is best left up to the individualized shared decision-making of clinicians and caregivers.

Nausea and Vomiting

Nausea and vomiting can be extremely uncomfortable and challenging to treat cancer symptom negatively impacting both patients and their families (Yee et al. 2018). Uncontrolled nausea and vomiting can have profound effects on the physical, cognitive, and psychosocial wellbeing of patients (Henson et al. 2020) and it is often “undertreated” (Vayne-Bossert et al. 2017). Between 20% and 70% of patients with advanced cancer have experienced nausea and vomiting (Harder et al. 2019). One survey of advanced cancer patients estimated that 22% of respondents had experienced nausea in the week just prior to survey administration (Harder et al. 2019).

Etiology

Like other symptoms (e.g. constipation), the etiology of nausea and vomiting is often difficult to determine and can be triggered by a multitude of cancer-related issues. Nausea and vomiting seems to be more common in patients actively receiving cancer treatments (i.e. chemotherapy and radiation) (Harder et al. 2019). It has been estimated that 80% of patients receiving radiation treatment experience nausea and/or vomiting (Yee et al. 2018). Current ASCO guidelines recommend that patients receiving anti-neoplastic agents be treated prophylactically with combination anti-emetic therapy according to the emetic risk of the administered drug(s) (Hesketh et al. 2020).

Many cancer patients experience nausea that is not associated with cancer treatments (i.e., radiation, chemotherapy, or surgeries) (Vayne-Bossert et al. 2017). Additional sources of nausea and vomiting in gastrointestinal cancers include decreased gastrointestinal motility, slow gastric emptying, constipation, malignant bowel obstruction, increased intracranial pressure (e.g., brain metastasis), metabolic derangements (e.g. hepatic failure, renal failure, hypercalcemia, hyponatremia), anxiety, depression, and many commonly used medications (Henson et al. 2020; Hesketh et al. 2020; Hisanaga et al. 2019; Navari 2020; Smith et al. 2012; Wickham 2020). Of note, ondansetron, a 5-HT3 receptor antagonist commonly given for cancer-related nausea and vomiting, is frequently administered in clinical practice without awareness of its constipating effects. Table 7 lists commonly used medications that may contribute to nausea and vomiting.

Table 7 Examples of common medications associated with nausea/vomiting (Henson et al. 2020; Navari 2020; Lacy et al. 2018; Wickham 2020).

Alpha 2 adrenergic agents
Beta blockers
Calcium channel blockers
Cannabis (cannabis hyperemesis syndrome)
Diuretics
Dopamine agonists
Hormones (estrogen/progesterone)
NSAIDs
Opioids
Oral iron
SSRIs
Sulfasalazine

Assessment

A thoroughly obtained history and physical exam is essential to determining the most likely etiology of nausea and vomiting and can appropriately guide treatment (Henson et al. 2020; Navari 2020; Wickham 2020). History should include assessing for signs and symptoms of constipation, temporal factors, comprehensive medication review, mitigating and intensifying factors and psychological symptoms (Wickham 2020). Physical exam should include a complete abdominal exam assessing for signs of ascites, obstruction, and/or masses along with a neurologic exam to rule out signs of vestibular dysfunction (e.g. nystagmus) and increased intracranial pressure (e.g. papilledema and focal neurologic deficits) (Navari 2020; Wickham 2020).

Treatment

Treatment for cancer-related nausea and vomiting should be largely driven by etiology. Anti-emetic drug regimens should be given as prophylaxis and treatment for chemotherapy and radiation-induced nausea/vomiting as established by published guidelines (e.g. ASCO, NCCN, MSSC) (Davis et al. 2021; Hesketh et al. 2020). Additionally, a meticulous review of potential offending medications should be undertaken whenever patients present with nausea and vomiting. Discontinuation of these medications may outweigh any potential benefit. In the case of opioid-induced nausea and vomiting, rotation to a different opioid medication may prove beneficial although evidence is limited (Sande et al. 2019). Allowing 48–72 hours for adjustment to any new opioid medication may result in improved tolerance of adverse effects such as nausea.

For patients with gastroparesis, delayed gastric emptying and or otherwise impaired gastrointestinal motility, prokinetic agents such as the D2 receptor antagonist metoclopramide may be particularly beneficial (Henson et al. 2020; Navari 2020; Wickham 2020). Metoclopramide also possesses anti-5HT3/5HT4 properties which may aid in its anti-emetic effect (Navari 2020; Wickham 2020). This medication should be avoided in patients with complete bowel obstruction due to risk of abdominal pain and viscous perforation and it carries with it a risk of developing extrapyramidal symptoms when used long term (Wickham 2020). Haloperidol is another commonly used D2 antagonist anti-emetic agent often used in cancer-related nausea and vomiting. Haloperidol may be particularly useful in drug-induced and metabolic causes of nausea and vomiting (Henson et al. 2020). Both metoclopramide and haloperidol are considered first-line anti-emetic agents for nausea and vomiting in advanced cancer by the MASCC (Davis et al. 2021).

Malignant bowel obstruction (MBO) can be a challenging cause of nausea and vomiting in gastrointestinal cancers. Traditionally, steroids (e.g. dexamethasone) and octreotide (a somatostatin analogue) have been used in the symptomatic management of MBO. Steroids may help with inflammation or edema associated with GI cancers and related obstructions (Wickham 2020). Octreotide may be helpful in reducing the gastrointestinal secretions and bowel motility that instigate related symptoms. Recently, however, research supporting the use of steroids and octreotide has been mixed (Davis et al. 2021; Krouse 2019).

Nonpharmacologic management of MBO should be considered in appropriate patient populations. While surgery is the "gold standard" of management of malignant bowel obstruction, many patients with advanced cancer are not candidates for surgery (Thampy 2020). Additionally, patients often fail medical management of MBO resulting in refractory symptoms. Venting gastrostomy tubes can be a safer alternative to surgical management with high procedural success rates and minimal complications (Thampy 2020). Although evidence is limited, according to one systematic review, over 90% of patients with MBO who underwent venting gastrostomy tube placement achieved some level of improvement in nausea and vomiting post procedurally when recorded by the studies (Thampy 2020).

Olanzapine is a second generation anti-psychotic medication that has shown growing promise in the treatment of both chemotherapy-induced nausea vomiting (CINV) and nausea/vomiting unrelated to the cancer treatment (Davis and Sanger 2020; Navari 2020; Navari et al. 2020; Sutherland et al. 2018). Additionally, olanzapine has now been proposed as a treatment for nausea/vomiting related to malignant bowel obstruction (Davis et al. 2021; Kaneishi et al. 2020; Navari 2020). Olanzapine antagonizes multiple nausea-related receptors including dopamine (D2), histamine (H1), muscarinic (M1), and serotonin (5HT) receptors (Davis and Sanger 2020; Smith et al. 2012). Of importance, a recent study suggested that olanzapine may be beneficial in improving overall quality of life related to improve appetite, improved overall well-being and decreased fatigue warranting additional study (Navari et al. 2020). The pilot trial has been replicated in a larger randomized trial at the Mayo Clinic (personal communication, Charles Loprinzi, June 2022). Olanzapine has recently been suggested as the first-line agent to improve cachexia and anorexia, and reverse weight loss in solid tumor patients by the American Society of Clinical Oncology (Roeland et al. 2023). Olanzapine may also be beneficial in the treatment of insomnia (Davis and Sanger 2020).

For patients with nausea and vomiting related to increased intracranial pressure, steroids in combination with palliative radiation for brain metastasis can be beneficial (Navari 2020; Wickham 2020). Suspected gastrointestinal reflux disease/gastritis contributing to nausea may warrant the use of proton pump inhibitors and H2 blockers (Navari 2020). For patients with suspected vestibular dysfunction, the use of antihistamines such as meclizine or cyclizine may be helpful (Henson et al. 2020; Navari 2020). Lastly, patients with suspected psychological contributors to nausea (e.g. anxiety/anticipatory nausea) may benefit from the introduction of a benzodiazepine such as lorazepam in addition to psychological therapies into their care plan (Navari 2020; Smith et al. 2012).

Oral Symptoms

Oral symptoms are common in cancer patients and can lead to significant impact on quality of life (Chen et al. 2021). In a study by Davies et al., the most commonly reported symptoms among their population of advanced cancer patients included dry mouth, taste disturbances and coating of the tongue followed by lip discomfort, "dirty mouth," and difficulty swallowing (Davies et al. 2021). Xerostomia, taste changes, and orofacial pain were noted to have the most significant functional impact on terminally ill cancer patients (Fischer et al. 2014). Research has also suggested that the majority of caregivers find addressing and evaluating the oral hygiene of their care recipients to be an important responsibility in the setting of terminal cancer diagnoses (Fischer et al. 2014).

Xerostomia

Xerostomia, or dry mouth, is the most commonly encountered oral symptom in cancer patients (Davies et al. 2021; Fischer et al. 2014). Etiologies include dehydration, chemotherapy, radiation, medications (e.g., anticholinergics, chemotherapy, opioids, diuretics, antidepressants), and mouth breathing (Millsop et al. 2017). Treatment is typically supportive with many patients experiencing subjective relief from small sips of water, ice chips, and moistened mouth swabs. Artificially sweetened chewing gums and candies can provide additional relief as can saliva substitute/saliva-stimulating mouthwashes and toothpastes (Millsop et al. 2017). For patients with xerostomia refractory to conservative management, pharmacologic options such as sialagogues can be trialed. These include pilocarpine and cevimeline but side effects may preclude continued use. Common adverse effects include gastrointestinal and cardiopulmonary effects and diaphoresis. Pilocarpine should be avoided in patients with glaucoma and both should be avoided in patients with asthma, uncontrolled hypertension, and gastric ulcers (Millsop et al. 2017).

Oral Mucositis

Oral mucositis is a common side effect of systemic chemotherapy and radiation treatments. Chemotherapy-induced mucositis typically manifests about one to two weeks after the start of chemotherapy and lasts the duration of treatment while the onset of radiation-induced mucositis is usually around the second to third week of radiation treatment and can continue for weeks postradiation therapy (Lalla et al. 2014). Oral mucositis involves painful inflammation of the oral mucosa often accompanied by ulceration. Conservative management includes the use of topical rinses, ice chips, and avoidance of irritating foods. There is insufficient evidence regarding the use of saline and bicarbonate oral rinses although these are relatively benign and may be trialed (Lalla 2020). Viscous lidocaine 2% rinses are available and are often mixed with additional agents including diphenhydramine and a coating agent (e.g. aluminum-magnesium hydroxide) (Lalla et al. 2008). Topical morphine oral solutions may also be trialed although recent evidence appears to be mixed (Nielsen et al. 2021). Patients with refractory pain related to oral mucositis often require systemic opioid treatment (Nielsen et al. 2021).

Oral Candidiasis (“Thrush”)

Patients with gastrointestinal cancers are at increased risk of oropharyngeal candidiasis also referred to as “thrush.” The use of antibiotics, corticosteroids, chemotherapy, and radiation therapy all contribute to an increased risk of developing thrush (Lerman et al. 2008). Thrush is most commonly caused by the organism *C. Albicans* and manifests as thick, white patches on the oral mucosa that can be removed with wiping to divulge underlying erythema (Lerman et al. 2008). Oncology patients with oral pain or discomfort should always be carefully evaluated for the development of thrush as this is largely a treatable condition with antifungal medications. Treatment for uncomplicated infections typically involves 10 days of Nystatin oral suspension (swish and swallow) or clotrimazole troches. Severe, refractory cases may require systemic antifungal treatments (Lerman et al. 2008). In hospice and palliative medicine patients with advanced cancer, the use of a single dose of 150 mg of oral fluconazole has proven subjectively and objectively effective and has been suggested as an alternative to multiday treatment to reduce overall oral burden and polypharmacy (Lagman et al. 2017).

Taste Changes

Taste changes are common in patients with cancer with 50% of patients receiving chemotherapy reporting changes in taste sensation (Braud and Boucher 2020). Taste changes may also be related to medications, underlying infection (e.g. oral thrush), radiation, renal disease, and gastroesophageal reflux (Braud and Boucher 2020). Treatment involves addressing the underlying dry mouth and infectious processes as well as removing offending medications (Braud and Boucher 2020).

Dysphagia

Dysphagia is common in the palliative care population and can be a distressing symptom for patients and their caregivers with evidence suggesting it negatively impacts quality of life (Tan et al. 2021). Addressing dysphagia begins with identifying its underlying etiology. Dysphagia can be classified into two anatomical categories: oropharyngeal dysphagia and esophageal dysphagia (Wilkinson et al. 2021). Oropharyngeal dysphagia is commonly the result of chronic neurologic conditions but may also be caused by oral conditions such as mucositis, poor dentition, and xerostomia often present in oncology patients. Esophageal dysphagia is very common in patients with advanced esophageal and gastric cancers due to malignant obstructions (Halpern and McCarter 2019). Additionally, immunocompromised patients may suffer from infectious esophagitis (e.g. HSV, CMV, or candida infection) and commonly used drugs such as nonsteroidal anti-inflammatory drugs and bisphosphonates may instigate pill esophagitis (Wilkinson et al. 2021).

Given the ubiquitous nature of opioid use in the treatment of cancer pain, opioid-induced esophageal dysfunction should also be considered on the differential. This condition is thought to arise from opioid-induced impaired esophageal motility, esophageal spastic contractility, and impaired gastroesophageal junction relaxation (Snyder and Vela 2020). It is associated with higher opioid doses and decreased doses of opioids may improve symptoms (Snyder and Vela 2020) although this may be an unrealistic option for patients with severe cancer-related pain.

Treatment for dysphagia depends on the underlying cause. It is important to identify patients who are approaching end of life to ensure appropriately informed goals of care discussions with patients and their caregivers regarding nutrition, hydration, and end of life care (Bodtke and Ligon 2016). Speech language pathologists can be especially helpful in the diagnostic workup of dysphagia and in assisting with recommendations for dietary modifications, optimizing swallow function, and providing education to patients and their caregivers (Bodtke and Ligon 2016). For patients in whom tumor obstruction is contributing to dysphagia, esophageal stenting may prove beneficial with over 95% of patients reporting an ability to tolerate liquids post procedure (Halpern and McCarter 2019). Stents may also be placed in the setting of gastric outlet obstruction often in patients with gastric cancer (Halpern and McCarter 2019). As always, the risks and benefits of any procedure must be carefully considered and discussed with patients and tailored to their individual oncologic situation.

Psychiatric Symptoms

Mood disorders, including major depressive disorder (MDD) and anxiety, occur in about 13% of medically ill individuals. Symptoms of depression occur in 58% of patients with cancer (Steinhauser et al. 2011). Further, mood disordered are frequently underdiagnosed and undertreated, which may lead to negative outcomes such as increased health care utilization, poor quality of life, increased interference with medical treatment, poor medical compliance, and increased morbidity and mortality. A previous metaanalysis showed that patients with cancer and depression are at 39% higher risk for death and patients with depressive symptoms were at 26% higher risk than patients without these symptoms (Satin et al. 2009).

When diagnosing psychiatric illness, there are two important principles to consider. First, the symptoms must cause significant distress or social or occupational dysfunction to qualify as a disorder. Second, all primary psychiatric illnesses are diagnoses of exclusion. Please see Table 8 for the diagnostic criteria for MDD per The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association 2013).

There are several questionnaires that may be helpful in the diagnosis of mood disorders: Patient Health Questionnaire-9 (PHQ-9) (Levis et al. 2019), Center for Epidemiologic Studies Depression Scale (CES-D) (Foelker and Shewchuk 1992), and Hospital Anxiety and Depression Scale (HADS) (Bjelland et al. 2002).

In patients with cancer, MDD may be challenging to diagnosis, as many of the symptoms of depression overlap with those of advanced malignancy. Depression itself may have somatic symptomology. The boundary between sadness and psychiatric illness is difficult to distinguish. It is also integral to distinguish depression from demoralization, as demoralization can happen commonly at different timepoints in a patient's illness. Please see Table 9 for characteristics of depression, demoralization, and grief.

Table 8 Diagnostic criteria for MDD.

Five or more out of nine symptoms (including at least one of depressed mood and loss of interest or pleasure) in the same 2-week period. Each of these symptoms represents a change from previous functioning.

1 Depressed mood
2 Loss of interest or pleasure (anhedonia)
3 Change in weight or appetite
4 Insomnia or hypersomnia
5 Psychomotor retardation or agitation
6 Loss of energy or fatigue
7 Worthlessness or guilt
8 Impaired concentration or indecisiveness
9 Thoughts of death or suicidal ideation or attempt

A key symptom to assess for the diagnosis of depression in this population is anhedonia. Advanced malignancy may lead to malaise, pain, and physical disability that would make participating in otherwise pleasurable activities unenjoyable. When considering this symptom as a diagnostic criterion for MDD, the anhedonia must be out of proportion to a patient's physical disability.

When evaluating a patient for psychiatric illness, common medical disorders must also be ruled out including: thyroid abnormalities, electrolyte abnormalities, kidney dysfunction, substance use disorders.

Treatment for MDD includes supportive psychotherapy, pharmacotherapy, or both. The combination of psychotherapy and pharmacotherapy provide more benefit than either intervention alone (Rakel 1999). There are several types of psychotherapy that have been proven useful for the management of MDD: cognitive behavioral therapy (CBT), interpersonal therapy, behavioral activation therapy, problem-solving therapy, psychodynamic therapy. Psychotherapy is associate with moderate decreases in depression scores (Okuyama et al. 2017).

There are various medication classes that can be considered for the treatment of depression and anxiety. Selective serotonin reuptake inhibitors (SSRIs), SNRIs, and TCAs are the most commonly used classes (Fournier et al. 2010). The patient's prognosis must be taken into account when beginning these medications, as benefit is not generally seen for at least 6–8 weeks. In patients with a very short prognosis and predominant depressive symptoms of low energy, psychostimulants (methylphenidate and dextroamphetamine) may be considered (Bahji and Mesbah-Oskui 2021). Please see Table 10 for pharmacotherapy pearls.

Advance Care Planning

Historically, advance care planning (ACP) did not begin until patients had a life expectancy of about 1 year. Only 23% of patients with cancer have ACP discussions with their oncologist; this percentage increases to 41% when patients with cancer are evaluated longitudinally by palliative care specialists (Thomas et al. 2019). Over the past several decades, a vast amount of research has been conducted on ACP with heterogeneous results. The mixed results of attempts to increase ACP and advance-directive completion may be partially due to the absence of a unified definition for this practice. A consensus definition of ACP was established in 2017: "[ACP] is a process that supports adults at any age or stage of health in understanding and sharing their personal

Table 9 Characteristics of grief versus demoralization versus depression (Block 2006; Robinson et al. 2015, 2016).

	Grief	Demoralization	Depression
Definition	Feelings and behaviors that result from a particular loss	Hopelessness, pointlessness, and helplessness caused by a loss of purpose and meaning in life	Depressed mood, decreased interest and pleasure, appetite and sleep disturbance, psychomotor agitation or retardation, decreased concentration, loss of energy, feelings of worthlessness, guilt, hopelessness, helplessness, and thoughts of death with impairment of functioning lasting at least 2 weeks
Symptoms and signs	Somatic distress, sleep and appetite disturbance, diminished concentration, social withdrawal, sighing	Hopelessness, lack of activities previously enjoyed, lack of interest, apathy, social withdrawal Can be measured with demoralization scale, 16-item patient list	Hopelessness, helplessness, anhedonia, worthlessness, guilt, suicidal ideation most useful diagnostic clues Somatic distress, sleep and appetite disturbance, diminished concentration, social withdrawal, sighing are also common
Other differentiating factors	Patient retains capacity for pleasure	Patient retains some capacity for pleasure	Nothing is enjoyable
	Comes in waves	If asked about family or pets, can mobilize interest and smartphone pictures	Constant
	Passive wishes for death	Apathy	Intense, persistent suicidal thoughts
	Able to look forward to the future	Not able to see much point to the past life or the future	No sense of anything to look forward to

Table 10 Pharmacotherapy for the management of depression in patients with cancer (Bruera et al. 1992; Forrest et al. 1977; Goldstein and Morrison 2013; Ostuzzi et al. 2018; Preskorn and Jerkovich 1990; Thase et al. 2007).

	Starting dose	Target dose	Onset of action	Advantages	Disadvantages/adverse effects	Dosing schedule
SSRIs						
Fluoxetine	10 mg	20–40 mg	4–8 weeks	Long half-life	GI side effects, decreased libido;	daily
Sertraline	25 mg in elderly; 50 mg in others	50–100 mg		Limited drug interactions	Headache; weight gain	
SNRIs						
Duloxetine	30 mg	60–90 mg		May be used for concomitant neuropathic pain	GI symptoms; caution in kidney and liver dysfunction	
Venlafaxine	37.5 mg	75–225 mg			GI symptoms, headache, somnolence; must be renally-dosed	
TCAs						
Nortriptyline	25 mg	50–100 mg			Delirium, constipation, dry mouth, sedation; caution in patients at high risk for anticholinergic effects	bedtime
Desipramine						
Psychostimulants						
Methylphenidate	2.5 mg	10–20 mg/day	<24 hours	Rapid onset of action; well-tolerated; improve appetite	Confusion, restlessness, anxiety, insomnia; caution in patients with cardiac disease	Take first dose after waking up and again after 4 hours
Dextroamphetamine	5 mg	10–30 mg/day				

values, life goals, and preferences regarding future medical care" (Sudore et al. 2017).

Discussing advance care planning and goals of care is integral when treating patients with cancer. These conversations should be started early in the patient's clinical course (Jain and Bernacki 2020). These conversations allow clinicians to learn about patient values and hopes. They also help clinicians determine what patients would find unacceptable for their care. Patients and family have greater confidence in the outcome of these discussions and decision-making when ACP is completed early (Dassel et al. 2021). Furthermore, surrogate decision makers experience less guilt, anxiety, and burden when they have had conversations regarding patient care preferences well before serious illness and end of life (McMahan et al. 2021). Table 11 shows basic communication strategies that can be used when discussing advance care planning.

Ethical Considerations

Ethical issues commonly arise in the care of the dying cancer patient. Balancing the principle of respect for patient and family autonomy with the principles of beneficence and non-maleficence can be difficult and often requires expert ethics consultation. The COVID-19 pandemic has underscored the need to also carefully consider the principle of justice in ethical decision making especially in situations of limited resources.

Ethical dilemmas frequently faced in end of life care include challenges pertaining to medically ineffective treatment at end of life, withholding and withdrawing life-sustaining treatments and patient/family refusal of pain-relieving medications (Riches and Voigt 2021). Additionally, ethical issues related to patient "truth telling" in terms of diagnosis and prognostication, requests for medical aid in dying, and issues related to assessment of decision-making capacity and identification of appropriate surrogate decision makers have been repeatedly cited in research (Schofield et al. 2021). Early palliative care intervention in advanced cancer patients including value based goals of care discussions may help patients more effectively plan for the future and avoid potentially inappropriate treatments at end of life which often result in ethical challenges (Parikh et al. 2013; Riches and Voigt 2021). See advance care planning section above.

Table 11 Communication strategies when discussing ACP.

Communication tool	Examples
Normalize	"I speak to all of my patients about what is important to them and the type of care they would want in the future if they got sick."
Explore values	"As you look to the future, what do you hope to accomplish?" "Were you to become very sick, what quality of life would be unacceptable for you?" "Tell me about what is most important to you."
Summarize values	"You have given me a lot of useful information. What I am hearing is…"
Recommendation	"Based on your goals and values, I recommend… How does that sound?"

Spirituality and End of Life

As patients approach end of life, spirituality and religiosity amass greater significance and can have substantial influence on quality of life (Delgado-Guay et al. 2011). Spiritual pain and existential distress are common (Delgado-Guay et al. 2011). Data suggests that spiritual support may improve care quality, decrease "aggressive" end of life care, and generate greater use of hospice resources (Delgado-Guay et al. 2011). A study conducted in the southwest United States revealed that 98% of advanced cancer patients surveyed identified as spiritual and or religious and that the majority of patients surveyed felt their spirituality/religiosity had a positive effect on coping with serious illness (Delgado-Guay et al. 2011).

Different spiritual practices can influence end of life decision making. It is important to take into consideration a patient's religious and spiritual practices and their impact on medical decisions. Consider asking patients, "Are you a religious or spiritual person? In what ways do your religious or spiritual beliefs influence decisions about your health?"

Some religions are more accepting of the natural disease trajectory of terminal illnesses than others. While some religions recommend against prolonging life in incurable disease, others have firm rules to guide decision making at end of life. Generally speaking, Christianity and Hinduism accept that death need not be prolonged unnecessarily in the setting of terminal illness and natural death may occur (Choudry et al. 2018). The interpretation of Islamic law varies widely throughout the world although the religion's emphasis on respect for dignity often allows for avoidance and withdrawal of life prolonging treatments including artificial nutrition and hydration when such treatments no longer provide comfort (Choudry et al. 2018). Judaism is complex and interpretation of Jewish law often diverges between rabbinical authorities. Orthodox Judaism typically views the provision of artificial nutrition and hydration at end of life as a necessity and often prohibits withdrawal of life sustaining treatments that have already been initiated (Choudry et al. 2018). Patients and families often turn to their rabbis for guidance and support in navigating these challenging end of life situations with their physicians (Choudry et al. 2018).

In our practice, spiritual care consultation can be particularly helpful not only in addressing goals of care and end of life planning but also in educating healthcare providers on the various end of life practices and rituals of different faith communities. For example, Muslim patients require a very timely burial while Roman Catholic patients often request Sacrament of the Sick aka “Last Rites” from a priest in their final hours (Choudry et al. 2018). Moreover, Sikh patients view hair as God’s gift and strongly prohibit the removal or cutting of hair on the body (Choudry et al. 2018). Recognizing the importance of different religious and cultural practices is key to providing high quality patient and family centered care.

Conclusion

Key Take Home Messages

1 Palliative Care increases both quality of life and survival in patients with cancer when it is provided early. It should be offered concomitantly with cancer-directed therapies.

2 Cancer-related pain is highly prevalent at all stages of disease, including during survivorship. This pain should be treated using a multimodal strategy including pharmacologic, behavioral, and interventional techniques.

3 Gastrointestinal symptoms such as constipation, nausea, vomiting, mucositis, and xerostomia are common; these symptoms may be caused by cancer-directed therapies and other medications, as well as the underlying malignancy. When treating these symptoms, it is best to determine the etiology first, as this will aid in dictating potential treatments.

4 Depression is one of the most under-recognized and undertreated disorders in patients with cancer. This should be screened for routinely. There should also be a low threshold to treat with pharmacotherapy and/or psychotherapy.

5 Religion and spirituality may be important sources of strength and support for patients with cancer. These beliefs should be elicited early in the course of disease, especially as some religions provide specific guidance on end-of-life care.

Areas for Further Research

1 Development of electronic secure Apps that can iteratively communicate preferences

2 Development of predictive markers of the efficacy and risks of combination analgesia

Trusted Websites for Further Reading

Center to Advance Palliative Care: www.capc.org
American Academy of Hospice and Palliative Medicine: www.aahpm.org
Fast Facts-Palliative Care Network of Wisconsin: www.mypcnow.org/fast-facts
National Comprehensive Cancer Network Supportive Care Guidelines: Supportive Care (nccn.org)
National Hospice and Palliative Care Coalition: www.nhpco.org

References

Aiyer, R., Mehta, N., Gungor, S., and Gulati, A. (2018). A systematic review of NMDA receptor antagonists for treatment of neuropathic pain in clinical practice. *Clin J Pain* 34 (5): 450–467. doi:10.1097/AJP.0000000000000547.

Alvaro, D., Coluzzi, F., Gianni, W. et al. (2022). Opioid-induced constipation in real-world practice: a physician survey, 1 year later. *Pain Ther*. Published online February 5. doi:10.1007/s40122-022-00354-4.

American Psychiatric Association and American Psychiatric Association (eds.) (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5e. American Psychiatric Association.

Apolone, G., Corli, O., Caraceni, A. et al. (2009). Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. *Br J Cancer* 100 (10): 1566–1574. doi:10.1038/sj.bjc.6605053.

Bahji, A. and Mesbah-Oskui, L. (2021). Comparative efficacy and safety of stimulant-type medications for depression: a systematic review and network meta-analysis. *J Affect Disord* 292: 416–423. doi:10.1016/j.jad.2021.05.119.

Berterame, S., Erthal, J., Thomas, J. et al. (2016). Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *The Lancet* 387 (10028): 1644–1656. doi:10.1016/S0140-6736(16)00161-6.

Bjelland, I., Dahl, A.A., Haug, T.T., and Neckelmann, D. (2002). The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res* 52 (2): 69–77. doi:10.1016/s0022-3999(01)00296-3.

Block, S.D. (2006). Psychological issues in end-of-life care. *J Palliat Med* 9 (3): 751–772. doi:10.1089/jpm.2006.9.751.

Bodtke, S. and Ligon, K. (2016). Dysphagia. In: *Hospice and Palliative Medicine Handbook: A Clinical Guide*, 106–107. CreateSpace Independent Publishing Platform.

Boland, J.W. and Boland, E.G. (2017). Pharmacological therapies for opioid induced constipation in adults with cancer. *BMJ* 358: j3313. doi:10.1136/bmj.j3313.

Braud, A. and Boucher, Y. (2020). Taste disorder’s management: a systematic review. *Clin Oral Investig* 24 (6): 1889–1908. doi:10.1007/s00784-020-03299-0.

Brooksbank, M. (2009). Palliative care: where have we come from and where are we going? *Pain* 144 (3): 233–235. doi:10.1016/j.pain.2009.06.010.

Bruera, E., Fainsinger, R., MacEachern, T., and Hanson, J. (1992). The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminary report. *Pain* 50 (1): 75–77. doi:10.1016/0304-3959(92)90114-Q.

Candy, B., Jones, L., Vickerstaff, V. et al. (2018). Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Pain, Palliative and Supportive Care Group, ed. *Cochrane Database Syst Rev* 2018 (6). doi:10.1002/14651858.CD006332.pub3.

Chen, X., D’Souza, V., Thomsen, T.A. et al. (2021). Oral health in adult patients receiving palliative care: a mixed method study. *Am J Hosp Palliat Care* 38 (12): 1516–1525. doi:10.1177/10499091211007449.

Choudry, M., Latif, A., and Warburton, K.G. (2018). An overview of the spiritual importances of end-of-life care among the five major faiths of the United Kingdom. *Clin Med Lond Engl* 18 (1): 23–31. doi:10.7861/clinmedicine.18-1-23.

Clark, D. (2007). From margins to centre: a review of the history of palliative care in cancer. *Lancet Oncol* 8 (5): 430–438. doi:10.1016/S1470-2045(07)70138-9.

Dassel, K.B., Towsley, G.L., Utz, R.L. et al. (2021). A limited opportunity: COVID-19 and promotion of advance care planning. *Palliat Med Rep* 2 (1): 194–198. doi:10.1089/pmr.2021.0013.

Davies, A., Buchanan, A., Todd, J. et al. (2021). Oral symptoms in patients with advanced cancer: an observational study using a novel oral symptom assessment scale. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 29 (8): 4357–4364. doi:10.1007/s00520-020-05903-1.

Davies, A., Leach, C., Caponero, R. et al. (2020). MASCC recommendations on the management of constipation in patients with advanced cancer. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 28 (1): 23–33. doi:10.1007/s00520-019-05016-4.

Davis, M., Hui, D., Davies, A. et al. (2021). MASCC antiemetics in advanced cancer updated guideline. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 29 (12): 8097–8107. doi:10.1007/s00520-021-06437-w.

Davis, M., Hui, D., Davies, A. et al. (2021). Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 29 (12): 8089–8096. doi:10.1007/s00520-021-06438-9.

Davis, M.P. and Sanger, G.J. (2020). The benefits of olanzapine in palliating symptoms. *Curr Treat Options Oncol* 22 (1): 5. doi:10.1007/s11864-020-00804-1.

De Giorgio, R., Zucco, F.M., Chiarioni, G. et al. (2021). Management of opioid-induced constipation and bowel dysfunction: expert opinion of an Italian multidisciplinary panel. *Adv Ther* 38 (7): 3589–3621. doi:10.1007/s12325-021-01766-y.

Deandrea, S., Montanari, M., Moja, L., and Apolone, G. (2008). Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 19 (12): 1985–1991. doi:10.1093/annonc/mdn419.

Delgado-Guay, M.O., Hui, D., Parsons, H.A. et al. (2011). Spirituality, religiosity, and spiritual pain in advanced cancer patients. *J Pain Symptom Manage* 41 (6): 986–994. doi:10.1016/j.jpainsymman.2010.09.017.

Canadian Agency for Drugs and Technologies in Health. (2014). *Dioctyl Sulfosuccinate or Docusate (Calcium or Sodium) for the Prevention or Management of Constipation: A Review of the Clinical Effectiveness*. Canadian Agency for Drugs and Technologies in Health.

Dzierżanowski, T. and Larkin, P. (2020). Proposed criteria for constipation in palliative care patients. A multicenter cohort study. *J Clin Med* 10 (1): E40. doi:10.3390/jcm10010040.

Fallon, M.T., Storey, D.J., Krishan, A. et al. (2015). Cancer treatment-related neuropathic pain: proof of concept study with menthol—a TRPM8 agonist. *Support Care Cancer* 23 (9): 2769–2777. doi:10.1007/s00520-015-2642-8.

Fischer, D.J., Epstein, J.B., Yao, Y., and Wilkie, D.J. (2014). Oral health conditions affect functional and social activities of terminally ill cancer patients. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 22 (3): 803–810. doi:10.1007/s00520-013-2037-7.

Foelker, G.A. and Shewchuk, R.M. (1992). Somatic complaints and the CES-D. *J Am Geriatr Soc* 40 (3): 259–262. doi:10.1111/j.1532-5415.1992.tb02079.x.

Forrest, W.H., Brown, B.W., Brown, C.R. et al. (1977). Dextroamphetamine with morphine for the treatment of postoperative pain. *N Engl J Med* 296 (13): 712–715. doi:10.1056/NEJM197703312961303.

Fournier, J.C., DeRubeis, R.J., Hollon, S.D. et al. (2010). Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* 303 (1): 47–53. doi:10.1001/jama.2009.1943.

Gibson, R.J. and Keefe, D.M.K. (2006). Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. *Support Care Cancer* 14 (9): 890. doi:10.1007/s00520-006-0040-y.

Gilron, I., Bailey, J.M., Tu, D. et al. (2005). Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 352 (13): 1324–1334. doi:10.1056/NEJMoa042580.

Gilron, I., Bailey, J.M., Tu, D. et al. (2009). Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet Lond Engl* 374 (9697): 1252–1261. doi:10.1016/S0140-6736(09)61081-3.

Gilron, I., Tu, D., Holden, R.R. et al. (2015). Combination of morphine with nortriptyline for neuropathic pain. *Pain* 156 (8): 1440–1448. doi:10.1097/j.pain.0000000000000149.

Ginex, P., Hanson, B., LeFebvre, K. et al. (2020). Management of opioid-induced and non–opioid-related constipation in patients with cancer: systematic review and meta-analysis. *Oncol Nurs Forum* 47 (6): E211–E224. doi:10.1188/20.ONF.E211-E224.

Goldstein, N. and Morrison, S. (2013). *Evidence-Based Practice of Palliative Medicine*. Saunders.

Griffiths, C., Kwon, N., Beaumont, J.L., and Paice, J.A. (2018). Cold therapy to prevent paclitaxel-induced peripheral neuropathy. *Support Care Cancer* 26 (10): 3461–3469. doi:10.1007/s00520-018-4199-9.

Guo, Y., Jones, D., Palmer, J.L. et al. (2014). Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. *Support Care Cancer* 22 (5): 1223–1231. doi:10.1007/s00520-013-2075-1.

Halpern, A.L. and McCarter, M.D. (2019). Palliative management of gastric and esophageal cancer. *Surg Clin North Am* 99 (3): 555–569. doi:10.1016/j.suc.2019.02.007.

Hanai, A., Ishiguro, H., Sozu, T. et al. (2017). Effects of cryotherapy on objective and subjective symptoms of paclitaxel-induced neuropathy: prospective self-controlled trial. *JNCI J Natl Cancer Inst* 110 (2): 141–148. doi:10.1093/jnci/djx178.

Hanson, B., Siddique, S.M., Scarlett, Y., and Sultan, S. (2019). American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology* 156 (1): 229–253.e5. doi:10.1053/j.gastro.2018.08.018.

Harder, S.L., Groenvold, M., Herrstedt, J., and Johnsen, A.T. (2019). Nausea in advanced cancer: relationships between intensity, burden, and the need for help. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 27 (1): 265–273. doi:10.1007/s00520-018-4326-7.

Hasson, F., Muldrew, D., Carduff, E. et al. (2020). "Take more laxatives was their answer to everything": a qualitative exploration of the patient, carer and healthcare professional experience of constipation in specialist palliative care. *Palliat Med* 34 (8): 1057–1066. doi:10.1177/0269216319891584.

Hawley, P.H. and Byeon, J.J. (2008). A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med* 11 (4): 575–581. doi:10.1089/jpm.2007.0178.

Henson, L.A., Maddocks, M., Evans, C. et al. (2020). Palliative care and the management of common distressing symptoms in advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue. *J Clin Oncol Off J Am Soc Clin Oncol* 38 (9): 905–914. doi:10.1200/JCO.19.00470.

Hershman, D.L., Unger, J.M., Crew, K.D. et al. (2018). Two-year trends of taxane-induced neuropathy in women enrolled in a randomized trial of Acetyl-L-Carnitine (SWOG S0715). *JNCI J Natl Cancer Inst* 110 (6): 669–676. doi:10.1093/jnci/djx259.

Hesketh, P.J., Kris, M.G., Basch, E. et al. (2020). Antiemetics: ASCO guideline update. *J Clin Oncol*. Published online July 13. doi:10.1200/JCO.20.01296.

Hisanaga, T., Shinjo, T., Imai, K. et al. (2019). Clinical guidelines for management of gastrointestinal symptoms in cancer patients: the Japanese society of palliative medicine recommendations. *J Palliat Med* 22 (8): 986–997. doi:10.1089/jpm.2018.0595.

Jain, N. and Bernacki, R.E. (2020). Goals of care conversations in serious illness: a practical guide. *Med Clin North Am* 104 (3): 375–389. doi:10.1016/j.mcna.2019.12.001.

Kanbayashi, Y., Sakaguchi, K., Ishikawa, T. et al. (2020). Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: a prospective self-controlled trial. *Breast Edinb Scotl* 49: 219–224. doi:10.1016/j.breast.2019.12.011.

Kaneishi, K., Imai, K., Nishimura, K. et al. (2020). Olanzapine versus metoclopramide for treatment of nausea and vomiting in advanced cancer patients with incomplete malignant bowel obstruction. *J Palliat Med* 23 (7): 880–881. doi:10.1089/jpm.2020.0101.

Krouse, R.S. (2019). Malignant bowel obstruction. *J Surg Oncol* 120 (1): 74–77. doi:10.1002/jso.25451.

Lacy, B.E., Parkman, H.P., and Camilleri, M. (2018). Chronic nausea and vomiting: evaluation and treatment. *Off J Am Coll Gastroenterol ACG* 113 (5): 647–659. doi:10.1038/s41395-018-0039-2.

Lagman, R., Davis, M., LeGrand, S. et al. (2017). Single-dose fluconazole therapy for oral thrush in hospice and palliative medicine patients. *Am J Hosp Palliat Care* 34 (7): 645–649. doi:10.1177/1049909116643927.

Lalla, R.V. (2020). Evidence-based management of oral mucositis. *JCO Oncol Pract*. Published online February 3. doi:10.1200/JOP.19.00766.

Lalla, R.V., Saunders, D.P., and Peterson, D.E. (2014). Chemotherapy or radiation-induced oral mucositis. *Dent Clin North Am* 58 (2): 341–349. doi:10.1016/j.cden.2013.12.005.

Lalla, R.V., Sonis, S.T., and Peterson, D.E. (2008). Management of oral mucositis in patients who have cancer. *Dent Clin North Am* 52 (1): 61–77. doi:10.1016/j.cden.2007.10.002.

Larkin, P., Sykes, N., Centeno, C. et al. (2008). The management of constipation in palliative care: clinical practice recommendations. *Palliat Med* 22 (7): 796–807. doi:10.1177/0269216308096908.

Larkin, P.J., Cherny, N.I., La Carpia, D. et al. (2018). Diagnosis, assessment and management of constipation in advanced cancer: ESMO clinical practice guidelines. *Ann Oncol* 29: iv111–iv125. doi:10.1093/annonc/mdy148.

LeFebvre, K.B., Rogers, B., and Wolles, B. (2020). Cancer constipation: clinical summary of the ONS guidelines^{TM} for opioid-induced and non-opioid-related cancer constipation. *Clin J Oncol Nurs* 24 (6): 685–688. doi:10.1188/20.CJON.685-688.

Lerman, M.A., Laudenbach, J., Marty, F.M. et al. (2008). Management of oral infections in cancer patients. *Dent Clin North Am* 52 (1): 129–153. doi:10.1016/j.cden.2007.10.006.

Levis, B., Benedetti, A., and Thombs, B.D. (2019). Accuracy of patient health questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *The BMJ* 365: l1476. doi:10.1136/bmj.l1476.

Loprinzi, C., Le-Rademacher, J.G., Majithia, N. et al. (2020). Scrambler therapy for chemotherapy neuropathy: a randomized phase II pilot trial. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 28 (3): 1183–1197. doi:10.1007/s00520-019-04881-3.

Loprinzi, C.L., Lacchetti, C., Bleeker, J. et al. (2020). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. *J Clin Oncol* 38 (28): 3325–3348. doi:10.1200/JCO.20.01399.

Matsuoka, H., Iwase, S., Miyaji, T. et al. (2019). Additive duloxetine for cancer-related neuropathic pain nonresponsive or intolerant to opioid-pregabalin therapy: a randomized controlled trial (JORTC-PAL08). *J Pain SymptomManage*58(4):645–653.doi:10.1016/j.jpainsymman.2019.06.020.

McMahan, R.D., Tellez, I., and Sudore, R.L. (2021). Deconstructing the complexities of advance care planning outcomes: what do we know and where do we go? A scoping review. *J Am Geriatr Soc* 69 (1): 234–244. doi:10.1111/jgs.16801.

McPherson, M.L.M. (2018). *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*, Second. American Society of Health-System Pharmacists.

Millsop, J.W., Wang, E.A., and Fazel, N. (2017). Etiology, evaluation, and management of xerostomia. *Clin Dermatol* 35 (5): 468–476. doi:10.1016/j.clindermatol.2017.06.010.

Moschen, A.R., Sammy, Y., Marjenberg, Z. et al. (2022). The underestimated and overlooked burden of diarrhea and constipation in cancer patients. *Curr Oncol Rep*. Published online March 24. doi:10.1007/s11912-022-01267-3.

Muldrew, D.H.L., Hasson, F., Carduff, E. et al. (2018). Assessment and management of constipation for patients receiving palliative care in specialist palliative care settings: a systematic review of the literature. *Palliat Med* 32 (5): 930–938. doi:10.1177/0269216317752515.

Nagashima M, Ooshiro M, Moriyama A, Sugishita Y, Kadoya K, Sato A, Kitahara T, Takagi R, Urita T, Yoshida Y, Tanaka H, Oshiro T, Okazumi S, Katoh R. Efficacy and tolerability of controlled-release oxycodone for oxaliplatin-induced peripheral neuropathy and the extension of FOLFOX therapy in advanced colorectal cancer patients. *Support Care Cancer*. 2014 Jun;22(6):1579–84. doi: 10.1007/s00520-014-2132-4. Epub 2014 Jan 24. PMID: 24452412; PMCID: PMC4008774.

Navari, R.M. (2020). Nausea and vomiting in advanced cancer. *Curr Treat Options Oncol* 21 (2): 14. doi:10.1007/s11864-020-0704-8.

Navari, R.M., Pywell, C.M., Le-Rademacher, J.G. et al. (2020). Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. *JAMA Oncol* 6 (6): 895–899. doi:10.1001/jamaoncol.2020.1052.

Nicholson, B. (2009). Benefits of extended-release opioid analgesic formulations in the treatment of chronic pain. *Pain Pract Off J World Inst Pain* 9 (1): 71–81. doi:10.1111/j.1533-2500.2008.00232.x.

Nielsen, B.N., Friis, S.M., Schmiegelow, K. et al. (2021). Evaluation of topical morphine for treatment of oral mucositis in cancer patients. *Br J Pain* 15 (4): 411–419. doi:10.1177/2049463720975061.

Okuyama, T., Akechi, T., Mackenzie, L., and Furukawa, T.A. (2017). Psychotherapy for depression among advanced, incurable cancer patients: a systematic review and meta-analysis. *Cancer Treat Rev* 56: 16–27. doi:10.1016/j.ctrv.2017.03.012.

Ostuzzi, G., Matcham, F., Dauchy, S. et al. (2018). Antidepressants for the treatment of depression in people with cancer. *Cochrane Database Syst Rev* 4: CD011006. doi:10.1002/14651858.CD011006.pub3.

Palliative Care Definition. What is palliative care. Accessed May 31, 2022. https://www.capc.org/about/palliative-care

Parikh, R.B., Kirch, R.A., Smith, T.J., and Temel, J.S. (2013). Early specialty palliative care — translating data in oncology into practice. *N Engl J Med* 369 (24): 2347–2351. doi:10.1056/NEJMsb1305469.

Preskorn, S.H. and Jerkovich, G.S. (1990). Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. *J Clin Psychopharmacol* 10 (2): 88–95. doi:10.1097/00004714-199004000-00003.

Rakel, R.E. (1999). Depression. *Prim Care Clin Off Pract* 26 (2): 211–224. doi:10.1016/S0095-4543(08)70003-4.

Riches, J.C. and Voigt, L.P. (2021). Palliative, ethics, and end-of-life care issues in the cancer patient. *Crit Care Clin* 37 (1): 105–115. doi:10.1016/j.ccc.2020.08.005.

Robinson, S., Kissane, D.W., Brooker, J. et al. (2016). Refinement and revalidation of the demoralization scale: the DS-II-external validity. *Cancer* 122 (14): 2260–2267. doi:10.1002/cncr.30012.

Robinson, S., Kissane, D.W., Brooker, J., and Burney, S. (2015). A systematic review of the demoralization syndrome in individuals with progressive disease and cancer: a decade of research. *J Pain Symptom Manage* 49 (3): 595–610. doi:10.1016/j.jpainsymman.2014.07.008.

Roeland, E.J., Bohlke, K., Baracos, V.E. et al. for the Cancer Cachexia Expert Panel. (2023). Cancer Cachexia: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol*. 12 June 2023.

Rome IV Criteria. Rome foundation. Accessed May 31, 2022. https://theromefoundation.org/rome-iv/rome-iv-criteria

Ruddy, K.J., Le-Rademacher, J., Lacouture, M.E. et al. (2019). Randomized controlled trial of cryotherapy to prevent paclitaxel-induced peripheral neuropathy (RU221511I); an ACCRU trial. *Breast Edinb Scotl* 48: 89–97. doi:10.1016/j.breast.2019.09.011.

Sande, T.A., Laird, B.J.A., and Fallon, M.T. (2019). The management of opioid-induced nausea and vomiting in patients with cancer: a systematic review. *J Palliat Med* 22 (1): 90–97. doi:10.1089/jpm.2018.0260.

Satin, J.R., Linden, W., and Phillips, M.J. (2009). Depression as a predictor of disease progression and mortality in cancer patients. *Cancer* 115 (22): 5349–5361. doi:10.1002/cncr.24561.

Schofield, G., Dittborn, M., Huxtable, R. et al. (2021). Real-world ethics in palliative care: a systematic review of the ethical challenges reported by specialist palliative care practitioners in their clinical practice. *Palliat Med* 35 (2): 315–334. doi:10.1177/0269216320974277.

Sera, L. and McPherson, M.L. (2018). Management of opioid-induced constipation in hospice patients. *Am J Hosp Palliat Care* 35 (2): 330–335. doi:10.1177/1049909117705379.

Seretny, M., Currie, G.L., Sena, E.S. et al. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain* 155 (12): 2461–2470. doi:10.1016/j.pain.2014.09.020.

Smith, E.M.L., Pang, H., Cirrincione, C. et al. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA J Am Med Assoc* 309 (13): 1359–1367. doi:10.1001/jama.2013.2813.

Smith, H.S., Smith, J.M., and Smith, A.R. (2012). An overview of nausea/vomiting in palliative medicine. *Ann Palliat Med* 1 (2): 10314–10114.

Smith, T.J., Temin, S., Alesi, E.R. et al. (2012). American Society of clinical oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol*. Published online February 6 . doi:10.1200/JCO.2011.38.5161.

Snyder, D.L. and Vela, M.F. (2020). Opioid-induced esophageal dysfunction. *Curr Opin Gastroenterol* 36 (4): 344–350. doi:10.1097/MOG.0000000000000648.

Steinhauser, K.E., Arnold, R.M., Olsen, M.K. et al. (2011). Comparing three life-limiting diseases: does diagnosis matter or is sick, sick? *J Pain Symptom Manage* 42 (3): 331–341. doi:10.1016/j.jpainsymman.2010.11.006.

Sudore, R.L., Lum, H.D., You, J.J. et al. (2017). Defining advance care planning for adults: a consensus definition from a multidisciplinary delphi panel. *J Pain Symptom Manage* 53 (5): 821–832.e1. doi:10.1016/j.jpainsymman.2016.12.331.

Sutherland, A., Naessens, K., Plugge, E. et al. (2018). Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. *Cochrane Database Syst Rev* 9: CD012555. doi:10.1002/14651858.CD012555.pub2.

Tai, S.Y., Lee, C.Y., Wu, C.Y. et al. (2016). Symptom severity of patients with advanced cancer in palliative care unit: longitudinal assessments of symptoms improvement. *BMC Palliat Care* 15: 32. doi:10.1186/s12904-016-0105-8.

Tan, L.L.C., Lim, Y., Ho, P. et al. (2021). Understanding quality of life for palliative patients with dysphagia using the swallowing quality of life (SWAL-QOL) questionnaire. *Am J Hosp Palliat Care* 38 (10): 1172–1176. doi:10.1177/1049909121992532.

Thampy, S. (2020). Safety and efficacy of venting gastrostomy in malignant bowel obstruction: a systematic review. *J Palliat Care* 35 (2): 93–102. doi:10.1177/0825859719864915.

Thase, M.E., Pritchett, Y.L., Ossanna, M.J. et al. (2007). Efficacy of duloxetine and selective serotonin reuptake inhibitors: comparisons as assessed by remission rates in patients with major depressive disorder. *J Clin Psychopharmacol* 27 (6): 672–676. doi:10.1097/jcp.0b013e31815a4412.

Thomas, T.H., Jackson, V.A., Carlson, H. et al. (2019). Communication differences between oncologists and palliative care clinicians: a qualitative analysis of early, integrated palliative care in patients with advanced cancer. *J Palliat Med* 22 (1): 41–49. doi:10.1089/jpm.2018.0092.

van den Beuken-van Everdingen, M.H.J., Hochstenbach, L.M.J., Joosten, E.A.J. et al. (2016). Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage* 51 (6): 1070–1090.e9. doi:10.1016/j.jpainsymman.2015.12.340.

Van Nimmen, N.F.J., Poels, K.L.C., Menten, J.J. et al. (2010). Fentanyl transdermal absorption linked to pharmacokinetic characteristics in patients undergoing palliative care. *J Clin Pharmacol* 50 (6): 667–678. doi:10.1177/0091270009347872.

Vayne-Bossert, P., Haywood, A., Good, P. et al. (2017). Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery). *Cochrane Database Syst Rev* 7: CD012002. doi:10.1002/14651858.CD012002.pub2.

Wickham, R.J. (2020). Nausea and vomiting: a palliative care imperative. *Curr Oncol Rep* 22 (1): 1. doi:10.1007/s11912-020-0871-6.

Wiffen, P.J., Wee, B., Derry, S. et al. (2017). Opioids for cancer pain - an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017 (7): CD012592. doi:10.1002/14651858.CD012592.pub2.

Wilkinson, J.M., Codipilly, D.C., and Wilfahrt, R.P. (2021). Dysphagia: evaluation and collaborative management. *Am Fam Physician* 103 (2): 97–106.

Yee, C., Drost, L., Zhang, L. et al. (2018). Impact of radiation-induced nausea and vomiting on quality of life. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer* 26 (11): 3959–3966. doi:10.1007/s00520-018-4286-y.

Yeh, C.H., Lukkahatai, N., Campbell, C. et al. (2019). Preliminary effectiveness of auricular point acupressure on chemotherapy-induced neuropathy: part 1 self-reported outcomes. *Pain Manag Nurs Off J Am Soc Pain Manag Nurses* 20 (6): 614–622. doi:10.1016/j.pmn.2019.04.005.

Yeh, C.H., Lukkahatai, N., Campbell, C. et al. (2019). Preliminary effectiveness of auricular point acupressure on chemotherapy-induced neuropathy: part 2 laboratory-assessed and objective outcomes. *Pain Manag Nurs* 20 (6): 623–632. doi:10.1016/j.pmn.2019.04.004.

Yenikomshian, M.A., White, A.G., Carson, M.E. et al. (2017). Projecting the cost, utilization, and patient care impact of prescribing extended release non-abuse-deterrent opioids to chronic pain patients. *J Opioid Manag* 13 (5): 291–301. doi:10.5055/jom.2017.0398.

28 Psychological Oncology and Wellbeing

Wellbeing (part 1) and narrative practices in child palliative care (part 2)

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Part 1 From Trauma to Transformation

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Background

A mentor once said to me, "*We all have the same journey; they are just nuanced versions of one another*." This remains an authentic reminder that we never know what another's journey may have been, or indeed what current challenges others contend with. The understanding that life's struggles can lead to positive changes and adaptations is widespread. Examples include: Viktor Frankl's (2006) work considering the development of meaning in life following an adversarial experience; Nietzsche's well-known assertion "*that which does not kill us, makes us stronger*" (Nietzsche as cited in Haidt 2006, pp.135); and Kierkegaard's reflections which discuss the importance of struggles for the development of existential freedom (Kierkegaard 1944).

The Japanese art of Kintsugi repairs a broken ceramic artifact with precious metals, transforming it into a new, unique object. Taking this art form as a mindset and philosophy, the beauty of a transformed object is found to lie in its imperfection and reparation. Kintsugi celebrates the broken pieces of an artifact returning to one another to become whole. This metaphor draws attention to the richness of the human condition, which is contributed to by joys, our disappointments, challenges, and losses (Boniwell and Tunariu 2019).

Theory of Shattered Assumptions

Janoff-Bulman's Theory of Shattered Assumptions (1992), claims that at the epicenter of an internal personal narrative are fundamental assumptions about safety and security. A profound shift in worldview and the destabilization of a personal sense of security has been described when the integrity of a personal framework and held assumptions are disrupted, i.e., by trauma (Janoff-Bulman 1992). In some individuals, the destabilization that occurs, in tandem with the restoration of a new worldview, can be the pivot from which posttraumatic growth (PTG) occurs. In essence, this theory illustrates how an individual creates a new personal narrative, while reconstructing their life and the world they inhabit. This draws similarity to the beauty of reconstruction, as seen in the practice of the art of Kintsugi.

Posttraumatic Growth

Alongside the negative consequences of adversity, we draw our attention to the potential positive transformational effects of adversity, which often exist alongside one another (Boniwell and Tunariu 2019). These have been termed benefit-finding, adversarial growth, or posttraumatic growth (PTG). PTG is defined as "*positive psychological changes experienced as a result of the struggle with traumatic or highly challenging life circumstances*" (Tedeschi et al. 2018, p.3). PTG is a subjective and individualizing process of struggling with trauma, and the change that arises as a result of the outcome of the trauma. PTG results in a shift in perspective such that an opportunity for growth and development may be borne out of trauma. In dealing with trauma, PTG may be experienced through both the transformation and reappraisal of life schema, in which an individual surpasses pre-existing levels of functioning (Tedeschi et al. 2018).

Most perspectives of PTG have consistently found that transformation or growth manifests in one or more of the following five domains: enhanced appreciation for life, increased interpersonal relationships, feeling a sense of personal strength, finding new possibilities, and spiritual/existential development (Tedeschi et al. 2018).

Corporeal PTG – A New Domain?

Hefferon (2012) proposed a novel model of Corporeal PTG (C-PTG) which evolved as a result of physical illness. This proposed model revealed an enhanced appreciation of the physical

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self, whereby the development of PTG was facilitated through new relationships and reconnection with the physical body.

PTG and Cancer

Those affected by cancer – patients, family, friends – have an intimate understanding that a cancer illness experience affects both the physical and psychological states. In addition to this, there is increasing recognition that alongside distress, patients may describe certain benefits arising from their experiences (Urcuyo et al. 2005).

The direct impact of cancer on the visible body causes changes such as fatigue, weight loss, and alopecia. Meanwhile, the psychological changes are invisible, internalized, and hidden from the onlooker. These physical and psychological changes are profound and are suggested to disrupt pre-existing frameworks, i.e., future view, goals, hopes, and identity (Hefferon 2012). Thus, it is the nature of the physical trauma and the impact it has on a multitude of an individual's internal and external characteristics that facilitates PTG or indeed, corporeal PTG. Thus drawing alignment with Janoff-Bulman's Shattered Assumptions Theory (Hefferon, 2013).

The Relationship between PTG and Meaning-Making

Tedeschi and Calhoun (1996) found that the search for meaning is often derived from experiencing and surviving trauma. Meaning has been identified through the reconstruction of core assumptions (Tedeschi et al. 2018). This comprises of two elements, presence of meaning, i.e., coherence (a purpose to one's existence) and a search for meaning, i.e., purpose (meaning in life) (Lomas, Hefferon and Itai Ivtzan, 2014). Active cognitive engagement with the search and presence of meaning (Tedeschi et al. 2018) supports an individual to rationalize traumatic experiences (Zeligman et al. 2019).

Facilitators of PTG

The Robert Wood Johnson Foundation set up the "positive health initiative" in 2008. This initiative conducted longitudinal research into health and wellbeing. Positive health encompasses specific health assets that have been found to improve health and illness. For example: positive emotions, hope, locus of control, optimism, purpose, positive relationships, and achievements. Positive health is considered as being a pathway to flourishing, encouraging a shift from illness to wellness, supporting the development of thriving after illness (Hefferon 2013; Seligman 2011).

Positive Emotions

Positive and negative emotions are not mutually exclusive – they can be felt simultaneously. An unexpected finding witnessed in those enduring distressing experiences is the presence of positive emotions. Such emotions are seen to provide protection and respite from the harsh reality of trauma, and in doing so, build resilience and resource. Positive emotions have also been found to be positive predictors for the development of PTG (Wehmeyer 2014).

Hope

Individuals who identify as being *high-hopers* reap far-reaching benefits, such as increased wellbeing, optimism, and effective coping strategies. In times of illness, those who are *high-hopers* exhibit more robust coping mechanisms supporting the development of a greater sense of control over illness (Taylor et al. 2000). The findings of Vellone et al. (2006) found that individuals experience a higher quality of life, less pain, and fewer physical symptoms following cancer diagnosis.

Locus of Control

Rotter's theory of locus of control (1966) proposes two dimensions; an internal locus of control (the understanding that we influence and control events of life), and an external locus of control (the understanding that we are unable to control events of life). Like high-hopers, those with an internal locus of control have been found to benefit from cognitive flexibility and perspective. These benefits include better posttrauma outcomes, increased ability to tackle challenges, increased resilience, ability to adapt, and develop new coping strategies (Zeligman et al. 2019). The demonstrated benefits observed in those with an internal locus of control suggest it is a positive influencing factor on the development of PTG (Zeligman et al. 2019).

Generating Narrative

Earlier in this part of the chapter, it was explained that coherence and purpose-finding are important parts of meaning-making. These phenomena are used to evaluate traumatic experiences. Husserl proposed the science of phenomenology (Hefferon 2013) whereby subjective, lived experiences are studied to provide meaning-making.

Narrative Therapy

Narrative practices have been shown to support individuals in developing stories around an illness experience supporting meaning-making. These practices have offered several positive outcomes, such as: improved recovery, enhanced coping mechanisms, meaning-making, and facilitating PTG (Tedeschi and Calhoun 2004). Narrative therapies are particularly beneficial for those who are not naturally inclined or find it difficult to verbalize their emotions (Lomas et al. 2014).

Creative Arts Therapy

Garland et al. (2007) created a six-week creative arts program (journaling, creative writing, and drawing) to encourage cancer patients to engage with their feelings around their experiences and find a novel vehicle to express these. Patients used art for the purposes of self-exploration to develop a narrative around their experiences. Reynold and Lim (2007) found that cancer patients were able to find meaning in their experiences through artistic expression, thus facilitating PTG through self-exploration.

Music Therapy

Magill (2000) found that music therapy offered potent benefits to cancer patients including improved physical symptoms.

Writing Intervention

Pennebaker's research (1997) showed that through structured writing sessions, meaning-making, and improved meta-cognition, significant benefits have been found in trauma populations. Structured writing sessions involve a commitment to engage with and write about a trauma experience for a period of 15–20 min. This research has been further extended to the cancer patient group, in which writing interventions have been shown to facilitate the development of PTG (Pennebaker and Chung 2011).

PTG and Wellbeing

The discovery of benefits borne from challenging experiences has been linked to greater levels of wellbeing and lower levels of depression (Helgeson et al. 2006). So, how is it that traumatic experiences positively impact our wellbeing?

The severity and significance of an event have little to do with supporting benefit-finding or PTG. In fact, it is the personal struggle of the experience with trauma that facilitates PTG. Similarly, wellbeing is increased through the mere act of seeking benefits, rather than what is perceived or experienced as being positive (Wehmeyer 2014). Dunn et al. (2009) found that wellbeing is increased if and when attention and focus are directed toward finding positive outcomes and benefits in times of adversity.

Wong (2009) introduced a new perspective to happiness – "chaironic happiness." Wong noted that a journey to enlightenment offers an elevated spiritual awareness, described as being exceptional, extraordinary, and unique. Encountering these transcendent experiences, which occur through struggles with challenge, suffering, and adversity, has been found to increase levels of wellbeing.

Positive Psychology Interventions

Gratitude

A study conducted by Emmons and McCullough (2003) found that people who practiced gratitude, i.e., counting their blessings over a 10-week period, reported better health, optimism, and pro-social behaviors. There are several ways in which gratitude may be practiced such as keeping a gratitude journal, writing thank you notes, and identifying "three good things."

Yoga

Yoga practice improves physical and mental health by improving levels of mindfulness and compassion and reducing stress. Studies have shown that the use of yoga in cancer populations has specifically been shown to improve fatigue, improve mental and physical wellbeing, increase tolerance of cancer symptoms, and improve cognition (Hefferon 2013).

Summary

As discussed earlier, there are several ways in which benefit finding may be encouraged in trauma survivors. For many, comfort and hope lie in the knowledge that experiencing PTG may indeed be a product of the struggle through adversity (Boniwell and Tunariu 2019).

It seems logical to therefore find appropriate ways to encourage trauma survivors to cultivate a positive mental framework. If suitable mechanisms are employed, there is potential for trauma survivors to reap the health benefits discussed in this chapter. This summary of benefits supports the author's call for PTG to be embedded in curricula for healthcare professionals caring for trauma survivors. It is crucial for survivors to have sufficient access to healthcare professionals who have the necessary skills and expertise to cultivate an environment in which the correct support can be signposted and offered.

A Note from the Author

It is prudent to be mindful that experiencing trauma is often difficult, painful, and can be debilitating. The aim is not to seek out trauma, far from it. However, in tragedy, it has been shown that when hope is retained, alongside the correct support mechanisms, there is opportunity. This chapter has discussed the significant benefits that may be derived from adversarial experiences from which there is potential to grow and transform. It is also important to highlight that positive psychology offers support in understanding the non-binary nature of life. The denial of negative emotions, distress, and avoidance of the reality of situations has been shown to have negative impacts on mental and physical wellbeing (Hefferon 2013).

The author offers understanding and support to all readers and trauma survivors, their loved ones, carers, and medical teams. The author is hopeful that in sharing knowledge, readers learn that although there is pain in experiencing adversity, there is potential for joy, positive transformation and growth to occur in tandem.

Summary Box

Facilitators of PTG in Cancer

- Positive emotions offer protection from the reality of trauma, supporting the development of resilience and resource.
- High hopers display robust coping mechanisms, fewer physical symptoms, and improved quality of life in ill health.
- An internal locus of control has been found to support the development of cognitive flexibility and perspective in times of illness.

Interventions

- Creating a narrative around lived experience has been shown to support the development of subjective meaning-making.
- Narrative therapy, creative arts therapy, music therapy, and writing interventions have been shown to be successful interventions that support the development of posttraumatic growth (PTG).
- Specific positive psychology interventions (PPIs) such as the practice of gratitude and yoga have been shown to improve health outcomes.

Areas for Further Research

1 This chapter has not considered the therapeutic benefit of coaching for cancer patients and cancer survivorship. Readers are encouraged to consider coaching as an important modality in such populations.

2 Coaching as a facilitator of PTG in cancer patients and cancer survivorship is an important area of consideration that requires further research.

Trusted Website for Further Reading

www.yourwellbeing.doctor

References

Boniwell, I. and Tunariu, A.D. (2019). *Positive Psychology: Theory, Research and Applications*. London: Open University Press.

Dunn, D.S., Uswatte, G., and Elliott, T.R. (2009). Happiness resilience and positive growth following disability: issues for understanding, research, and therapeutic intervention. In: *Oxford Handbook of Positive Psychology*, 2e (S.J. Lopez and C.R. Snyder), 651–664. New York; Oxford: Oxford University Press. 2011.

Emmons, R.A. and McCullough, M.E. (2003). Counting blessings versus burdens: an experimental investigation of gratitude and subjective well-being in daily life. *J Pers Soc Psychol* 84 (2): 377–389.

Frankl, V.E. (2006). *Man's Search for Meaning*. Boston: Beacon Press.

Garland, S.N., Carlson, L.E., Cook, S. et al. (2007). A non-randomized comparison of mindfulness-based stress reduction and healing arts programs for facilitating post-traumatic growth and spirituality in cancer outpatients. *Support Care Cancer* 15 (8): 949–961.

Haidt, J. (2006). *The Happiness Hypothesis: Finding Modern Truth in Ancient Wisdom*. New York: Basic Books.

Hefferon, K. (2012). Bringing back the body into positive psychology. *The Theory of Corporeal Posttraumatic Growth in Breast Cancer Survivorship*. *Psychology* 3 (12): 1238–1242.

Hefferon, K., Open University Press and Mcgraw-Hill Education (2013). *Positive Psychology and the Body: The Somatopsychic Side to Flourishing*. Maidenhead: Open University Press /Mcgraw-Hill Education.

Helgeson, V.S., Reynolds, K.A., and Tomich, P.L. (2006). A meta-analytic review of benefit finding and growth. *J Consult Clin Psychol* 74 (5): 797–816.

Janoff-Bulman, R. (1992). *Shattered Assumptions: Towards a New Psychology of Trauma*. S.L.: Simon and Schuster.

Kierkegaard, S. (1944). *The Concept of Dread*. New Jersey: Princeton University Press.

Lomas, T., Hefferon, K., and Ivtzan, I. (2014). *Applied Positive Psychology: Integrated Positive Practice*. Los Angeles: Sage.

Magill, L. (2000). The use of music therapy to address the suffering in advanced cancer pain. *J Palliat Care* 17 (3): 167–172.

Pennebaker, J.W. (1997). Writing about the emotional experiences as a therapeutic process. *Psychol Sci* 8 (3): 162–166.

Pennebaker, J.W. and Chung, C.K. (2011). Expressive writing: connections to physical and mental. In: *The Oxford Handbook of Health Psychology* (ed. H.S. Friedman), 417–437. Oxford University Press.

Reynold, F. and Lim, K.H. (2007). Turning to art as a positive way of living with cancer: a qualitative study of personal motives and contextual influences. *J Posit Psychol* 2 (1): 66–75.

Rotter, J.B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychol Monogr General Appl* 80 (1): 1–28. Available at: https://psycnet.apa.org/record/2011-19211-001 (accessed 10 March 2022). [online].

Seligman, M.E.P. (2011). *Flourish: A New Understanding of Happiness and Well-being – And How to Achieve Them*. London; Boston: Nicholas Brealey Publishing.

Taylor, S.E., Kemeny, M.E., Reed, G.M. et al. (2000). Psychological resources, positive illusions, and health. *Am Psychol* 55 (1): 99–109.

Tedeschi, R.G. and Calhoun, L.G. (1996). The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. *J Trauma Stress* 9 (3): 455–471.

Tedeschi, R.G. and Calhoun, L.G. (2004). Posttraumatic growth: conceptual foundations and empirical evidence. *Psychol Inq* 15 (1): 1–18.

Tedeschi, R.G., Shakespeare-Finch, J., Kanako, T., and Calhoun, L.G. (2018). *Posttraumatic Growth: Theory, Research and Applications*. New York, NY: Routledge.

Urcuyo, K.R., Boyers, A.E., Carver, C.S., and Antoni, M.H. (2005). Finding benefit in breast cancer: relations with personality, coping, and concurrent well-being. *Psychol Health* 20 (2): 175–192.

Vellone, E., Rega, M.L., Galletti, C., and Cohen, M.Z. (2006). Hope and related variables in Italian cancer patients. *Cancer Nurs* 29 (5): 356–366.

Wehmeyer, M.L. (2014). *The Oxford Handbook of Positive Psychology and Disability*. Oxford: Oxford University Press.

Wong, P. (2009). Existential psychology. In: *The Encyclopedia of Positive Psychology* (ed. S. Lopez), 361–368. Chichester: Blackwell Publishing Ltd.

Zeligman, M., Grossman, L., and Tanzosh, A. (2019). Posttraumatic growth in trauma survivors: meaning making and locus of control. *J Couns Psychol* 10 (2): 1–21.

Part 2 Narrative Practices in Child Palliative Care

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Background

Narrative practices (White and Epston 1990) are used to support families and children with cancer and who may die from cancer. These practices follow many of Amrita Sen Mukherjee's ideas of wellbeing (Part 1). Narrative therapy is a form of psychotherapy that seeks to help people identify their values, skills, and particular knowledges so they can better live their lives and effectively confront problems they face. During difficult yet precious journeys of child oncology and palliative care, I seek to help each family co-author new narratives about themselves and help the children make legacies. As stated by David Epston (www.narrativeapproaches.com), narrative therapy *"conversations can shape new realities and meanings of our lives."*

Narrative therapy legacy work needs a community. I thank the families and children, the oncology and palliative care teams, narrative therapists' consulted, and my supportive family and friends. This chapter is dedicated to the children who created beautiful legacies and to their families who found ways that these legacies could live on. My hope is that this work will lead to consideration of narrative practices in pediatric health, palliative care, and bereavement.

Introduction: Life as an Identity Project

When I visited Angy,[1] (aged 14), after she was told the cancer treatments weren't working, she said: "*I don't want to talk about dying.*" I responded: "*Would you like to talk about living and how you plan to live the rest of your life?*" This conversation gave me the idea of using narrative collective ideas I learned from David Denborough (Denborough 2008) to make legacies. There are many other narrative practices that are used in this work, such as preferred story development (Morgan 2000), re-authoring (White 1998), definitional ceremonies (Myerhoff 1982), re-membering (Hedtke 2014), and therapeutic documentation (Pilkington 2018). As well, I frequently use the following two child narrative therapy books to help me in this work (Freeman et al. 1997; Marsden et al. 2016).

According to White (2001), life is an identity project which is a public and social achievement. Narrative therapists believe that life is multistoried. We can be selective in what stories we find meaningful, sometimes retaining negative identity stories when there are troubles (White 2007). We follow the practice of developing identity by searching for stories that *counter* the problem story (Epston 2016), while acknowledging and respecting the very legitimate story of struggles.

Identity is strengthened by sharing. To help stories become social, "spreading the news" was a major part of the program I codeveloped with the children and families. Even when a child is terminally ill and has stories of pain and hardship, I discovered ways to voice stories of celebration of life, such as: life as an adventure, of appreciating loved ones, of courage, of living for each moment. These stories create art, music, writings, and films. The telling and retelling of these stories about their special knowledges, hopes, and dreams for life are what make legacies. White (2006) suggested it was important to explore how children respond to problems. These ideas helped me find hope in place of despair.

Blueband-Langner's (1978) observations support White's ideas that young children make meaning. Children almost always know when they have a terminal illness regardless of whether it is discussed with "open-awareness" or "mutual-pretense" (Blueband-Langner's term for when there's difficulty talking openly about death).

COURAGE Community

One challenge was handling with delicacy the experience of devastation felt after hearing that treatments have not worked. Families found it difficult to experience any other story than the very negative story. There was a subtlety of timing because if one talks too soon about the idea of "leaving a legacy," then people could feel that their story of difficulty was not heard. I never knew which child I worked with would die. Thus, a complete program was created so that legacies would be made all the time: the C.O.U.R.A.G.E. (**C**ancer as an **O**pportunity to **U**nite and share **R**esources in an **A**micable **G**roup setting that provides **E**ncouragement) community. This community was constantly providing possibilities for legacy (see Moxley-Haegert 2012, 2015; Moxley-Haegert and Moxley Haegert 2019). With narrative practices we worked for **community, compassion, cooperation, and hope.** Courage is a word used both in English and French. The need for bilingualism where I developed these narrative practices (Montreal Children's Hospital, Quebec, Canada) was a challenge, but also a creative endeavor. Our project titles made sense in both languages.

Our yearly COURAGE program consisted of monthly "Tree of Life" multiple family workshops (Ncube 2006); "Journey of a Lifetime" groups (based on McPhie and Chaffey 1998); and "satellite" groups making plans to keep hope alive for newly diagnosed children and families. There were weekly "questions of hope" to find special knowledges, abilities, values, and beliefs, which were placed on drawings that the younger children could color while the older children and parents responded. Example questions are: What will help you live better with change? What helps you find hope during difficult times? When permission was granted, responses were translated so their wisdoms could be sent to all members of our "virtual group" (nearly 200 families gave their email address so that wisdoms could be shared to create community).

We used narrative questions to lead the discussions and plan the legacies. Establishing stories of mastery and coping can be like creating islands of safety. This helps the child stand in a different space in relationship to the problem, and we can examine the problem story without re-traumatizing the child in our effort to help. The children and parents presented so many ideas about overcoming their storms of life that I created several different collective "living documents" (Newman 2008), which grew and changed, and were shared with others.

Ideas for Living-Hopework

When a child was told that treatments failed, it was necessary to participate in a lot of work, not just preparing for death but preparing for life.

Examples:

Megan tried to survive her third cancer but had to stop chemotherapy. She did not talk of dying, but when we did the family Tree of Life in her home, she had nothing on her branches (hopes, dreams, and aspirations), indicating that she knew she was dying. She asked if it was harmful not to talk about what was happening. I asked: "*What are your thoughts?*" She said: "*It is better to enjoy life.*" Megan left many legacies. She had years of responses to COURAGE questions of hope and art projects. Her voice can be heard reading a children's collective document in my Dulwich Centre presentation (Moxley-Haegert 2012).

Raphael demonstrated such special knowledges with his story. We knew that he was dying from his brain tumor, but his parents were not in agreement about talking openly about death. He told me a dream in which he was dying in a fire and his mother wouldn't save him. We had a "de-constructing conversation" (Pilkington 2017) about this dream and decided that if he was in such a situation and his mother didn't save him, it was that his mother *couldn't* save him (this discussion could be an example of "mutual-pretense"). He and his family attended Disneyworld for his special wish. He managed one day before he became so sick that they called emergency services. The emergency responders were firefighters. Raphael, said, "*I am dying, maman, and you can't save me.*" His mother was so happy that we had had the dream conversation so they could speak about death that night with "open awareness." (Blueband Langner's 'mutual pretence' and 'open awareness' 1978)

Laurence and her mother wrote a poem and music therapist, Christelle Jacquet, helped make it a song. Laurence sang and made a beautiful slide story. Laurence did not survive her third cancer.

Laurence's song (free translation from French – FTFF)

It is many years since I have known
that science has failed, and the cancer has grown.
There are some of you who have come to see,
what will happen, what will be?

Refrain: Oh, the suffering, when I think, and you know,
at what price, and how important it is,
THAT I AM ALIVE!

And I imagine that there might be a day,
when I can live the same way as I lived before,
for every moment I live, I say to myself,
I have a chance. Oh yes, but how?
[Refrain]

For every moment I live,
I would live another.
My name is Laurence. I am determined.
My strength, my energy, the serenity – diminished.
I think every morning I wake, how important it is to remember,
for every moment I live, this is not the end.
[Refrain]

I take my path. I get up each morning,
I continue to live without thinking, without forewarning.
I continue to live my life the most beautiful possible.
My next years will be or not. Whatever!
[Refrain]

Nothing will stop me. I am Laurence.
I am determined to live my life in the best way possible.
In the years to come,
JUST WATCH ME DANCE. I LOVE YOU ALL.

Bereavement

What Some Parents Found Not so Helpful in Bereavement Work

I learned that some parents who had been involved with grief groups teaching some contemporary ideas felt they were doing something wrong if they did not follow the stages of grief – denial, anger, bargaining, depression, and acceptance (Kubler-Ross 1969); or as suggested to certain parents in contemporary grief groups attended, if they did not believe that they needed this experience to gain certain knowledge; or felt that they did not want to disengage from the relationship (Freud 1961). Assumptions not always appreciated included accepting the "reality" of death; promoting deathbed conversations to say goodbye; completing "unfinished business," and planning to "move on" (some of what parents found unhelpful was supported by Stevenson 2014).

Narrative Ideas for Bereavement

In *Little Steps* book (*Petits Pas* – in French) (https://www.hopitalpourenfants.com/sites/default/files/PDFs/petit_pas_lr.pdf. 2014), Sylvie (mother of Pierluc) wrote (FTFF):

> Pierluc cherished one dream, that of swimming with the dolphins. The Wish Foundation helps children have a wish, but the cancer progressed so quickly that he left us a few days before the trip. When the doctors told us that he only had a few hours to live, I slept at his side and told him to close his eyes and I told him of the dream trip he was supposed to have taken. Pierluc smiled and saw very well in his imagination.

Sylvie felt he was at peace. However, she was not. I dreamt Pierluc told me to call his mother (in perfect English although he spoke only French). I called Sylvie and she was having a difficult time. She had lost the COURAGE program community when Pierluc died. Friends whose children survived seemed not to know how to interact with her now. I began to consider forming a narrative therapy bereavement group which followed narrative therapy ethics of reengaging, keeping the loved one close, keeping stories alive, bringing the best of the past into the future, and inviting stories other than grief.

Re-membering

White (2006) used the metaphor of life as a "club" that includes significant members of the past, present, and future. When someone dies, the relationship with the loved person is NOT lost. Guided by the metaphor "Saying Hullo Again" one can help parents to re-establish the relationship with the child that they might have lost when the child dies (White 1988). In certain narrative letters sent after the death of a child, re-membering questions were added (see Moxley-Haegert 2012).

Counter-Storying

Listening for subordinate stories helps people to distance themselves from the realities of the problems and to focus on other realities that are also present, but relatively unavailable (White and Epston 1990). The "Little Steps" document was inspired by the narrative practice of counter-story development which recognizes not only the stories of these parents' challenges to survive the death of a child but also the stories of the competences, special abilities and knowledges. Here is an example.

> Linda: *I heard a counter-story during a conversation with Sylvie. Antoine (a fellow cancer patient and a friend of Pierluc's – not his real name) went to swim with the dolphins on his Wish Foundation trip. Sylvie asked if they would bring a picture of Pierluc on a toy dolphin so Pierluc could also visit the dolphins. The dolphins played with the toy dolphin for a long time. Sylvie was able to bring Pierluc closer to her heart and soul. She began to realize that her stories were not only of loss and sadness. She had a counter-story of this new ability to see joy and appreciation.*

Definitional Ceremony

To accompany this project of identity reconstruction, the parents creating the souvenir album "Petits Pas/Little Steps," were making definitional ceremonies through which a re-narration of stories promotes the development of rich stories that recognize and value life. The objective was to help parents renegotiate their earlier conclusions about identity that were weakened with the death of a child (definitional ceremonies were also used with the children (Moore et al. 2015)).

> Sylvie1(FTFF): *Two years after Pierluc's death, I enrolled in the Huma Ecuador Challenge with LEUCAN (fight against cancer). This challenge tested me in every imaginable way. I realized I still had a taste for life.*

Collective/Community Practices

Through various collective practices (see David Epston www.narrativeapproaches.com, who first developed collective practices through the anti-anorexia leagues, and Dulwich Centre https://dulwichcentre.com.au/collective-narrative-practice), the narrative therapist works with families to find stories of hope that would help them better manage these tragedies with the intent of finding ways that the child's presences might remain. The children were encouraged to use narrative collective ideas to make legacies and allow for subordinate stories to emerge so their legacies could continue to live on in the hearts of their families and friends.

Community was developed with our Little Steps Programme which is characterized by a criss-crossing exchange of stories and messages. These contain hard-won knowledges about ways of responding to tough times with stories and messages describing family initiatives, skills, values, and dreams that are implicit in these stories or messages.

> *A group of mothers used 'scrapbooking' as a form of narrative therapy for grief. Each child has its proper story. 'Little Steps' is a memory album of all the stories accompanied by words of comfort, of hope and counsel developed by parents in grief to help and support other parents who have had a child die. Written and created by a group of mothers whose child was treated at the Montreal Children's Hospital (Montreal, Quebec, Canada), and edited by Linda Moxley-Haegert and Marie-Claude Proulx, this album 'Little Steps' is an amazing work of love.* (https://www.hopitalpourenfants.com/sites/default/files/PDFs/petit_pas_lr.pdf. 2014)

The project began with a document suggesting that when such a catastrophe as the death of a child occurs, we can wonder how to make sense of it all. Since humans use language to tell stories and narrative practice focuses on stories to cope with strong emotions, we hope to manage these emotions in this group by sharing our stories with others. This project united parents living the death of a child in sharing their special knowledges and creating tools to help other parents living this experience. In this way, we implemented the knowledge of what parents had not found helpful and the knowledge of what was felt could be helpful from narrative practice. This was a different identity project.

Questions were developed with the help of other narrative therapists and parents consulting me to bring the child who had died closer to their hearts. These were questions concerning the physical, the place; memories; stories, missing /lamenting; culture; and the spiritual (spirituality was also used with the children, see Moore et al. 2020).

To help with this identity project we planned a "telling" of survival stories in written and artistic form. Re-tellings can thicken the story, making a positive re-grading of earlier conclusions about identity. The "Little Steps" project followed the practice of searching for hope stories and new identity knowledges. These new identity knowledges became social and public realizations.

Two mothers were overheard to say: "*In aiding others I realized that I helped myself*" (FTFF). They were asked if they would be willing to explain in more detail what they meant by this statement. This was Martine's answer (FTFF).

> Thank you for directing our project with such dedication and organization and compassion. When Linda asked me to be part of this project, at first it was hard and then I realized we were being led by hope. I hope with this project I will lead others to want to help themselves while helping others.
>
> When I think about the project "Little Steps" I feel that ….I was helped to create something which was healing. I felt I was able to let go of these cowardly feelings of never recovering and I could then give birth to another baby in this creation.

Co-research

To try to understand how palliative care and bereavement families viewed narrative practices, four parents and I codeveloped the following questions about our work together:

- What would you say was important to you in the therapy provided to you during your time of grief? What did you most appreciate in the work?
- How would you describe what was meaningful to you?
- Were any narrative methods used to help you in the process of managing grief useful, and if so, how?
- What could have been done differently in this work?

A collective document presents some of the responses of 15 family members (collective documentation – Denborough 2008). The themes developed are narrative therapy terms which present some of the hopes and dreams of the described outcomes from narrative therapy conversations and community practices (for complete document see Moxley-Haegert and Moxley Haegert 2019).

These questions and responses are termed primary research in narrative communities, that is, questions for therapeutic purposes as well as research purposes.

Some Ways in Which the Narrative Palliative Care Work Was Received

Collective Document – "us" refers to the parents of children who have died.

What Sustains Us through Hard Times?

Many of us have confronted what could be called the greatest tempest of our lives: the death of a child. Sometimes these storms seemed like a hurricane and produced such hard times.

We are mothers and fathers and siblings with a family member, a child, who died, and we worked hard to discover what could sustain us through this most difficult time in our lives.

It was not easy to survive the death of a child in our family, but we have worked to keep going during very difficult times. We have been thinking about all our special abilities and special knowledges that have helped us face so many problems during these tempestuous times. We have thought about all that has helped us keep hope alive during this greatest challenge of our lives. The questions in narrative therapy helped us find our ways of survival.

"Some of us felt that we lost our identity when our child died."

Life as an Identity Project

> Sylvie2 (FTFF)*: For me, working on the French in - Linda's manuscript for her French grief counselling book chapter (*Moxley-Haegert 2018*) has really helped me to find closure and turn the page, as well as giving me a more concrete sense of our individual meetings and permit a new reflection. What really touched me in the text were the explanations of the need of humans for self-identity. It is certain that after the death of a child, we ask ourselves if we are still a parent. It has been hard to respond to the questions of who is in our family when we meet people.*

Some of us felt that the project Little Steps helped us find our identity again and refocused our direction in life. Others found identity in different narrative practices.

Some of us had difficulty in finding a meaning in these experiences**.**

Meaning-Making

> Maude (FTFF): *I attended a group for bereaved parents, and they wanted me to find meaning in the experience. I did not have to have my son die in order to understand that I was a strong person. No one involved with the Little Steps project seemed to expect me to find meaning and yet in the process I learned so much about myself and what I want with life.*

Many of us realized that making meaning of this difficult time was important for us in our healing but it had to come from ourselves and not forced by others.

Some of us found that it greatly helped to have a supportive community around us. For some of us that was difficult, but the narrative therapy we received helped us develop community when it was not there naturally.

Some of us found it so helpful to find ways to continue the memory of our child so our child will not be forgotten. For some of us remembering came through re-membering conversations with Linda. For others, it was through creating *The Little Steps* book or the Tree of Life, and for others it was in the creation of legacies by our children. Linda also took pictures and filmed our projects and sent us every copy of them as well as all the "questions of hope" our child answered.

Re-membering

> Jackie *What I really liked was the letter written by Linda and Kelsey. They collected memories from the team to put in the letter. It reminded me of some of the good times in hospital with my son. Thank you.*
>
> Some of us began our healing by keeping our children close to our hearts which was keeping our relationship with them alive.

Some of us found help in finding another story other than just the story of our pain.

Double Stories

We found that there was often more than just the hurt and pain.

> Harris-Dean's family: *We appreciated the stories that some of the after-therapy questions helped develop. We found a lovely memory regarding Harris-Dean's only outing during which he wore a snowsuit for the first and only time. We remembered that it was a time of concern and worry because he was going to another hospital for an intervention. After-therapy conversation, we were able to remember his snowsuit and appreciate that he got a chance to wear (one) and that there were other ways to remember that outing. We appreciate that (this)remembering brought Harris Dean more into our lives.*

Community Building

> Jimmy: *I appreciated Linda coming to our home to do the Tree of Life with my family. We would have preferred to do it with other families. Both my wife and daughter, Megan were dying of cancer and could not easily leave home. My wife was so happy to strengthen our family togetherness while creating as a family. Now I am so happy to have that legacy of our family when my wife and daughter were alive.*

Some of us received support from the community of other bereaved parents while others found community within the family.

> Laura (FTFF) (sister, age 13*): I was ten when my brother died. I have kept and appreciated the memory box that Linda and I made. I appreciated it when Linda went to my school and helped me explain to my class what it feels like to have a brother sick for many years of cancer, then die. Linda helped the teachers understand that it is as hard to manage after a brother died as when a brother is sick. She explained that everyone manages grief uniquely, that there is no 'should' in how one manages it.*

Pay It Forward

> Angy's parents hosted a gala and raised an inspiring $135,000 for our hospital. In her address, Angy's mother quoted from the Angy's written narrative: *Even as she neared the end of her fight Angy had said "I want to talk about life and not about death."* (Chez Nous/At Home, 2010).

What Could Be Done Differently

> Martine (FTFF). "*There is nothing I would have wanted done differently (FTFF).*"

Appraising the Ethics of This Practice

Delicacy

Sometimes parents do not want their child to know what the medical professionals say about prognosis. The concept of "open-awareness" and "mutual-pretense" was discussed previously. When the parents and child can discuss the likelihood of death, then I openly discuss this with them. The legacy is named exactly what it is. We can plan, like with Angy, the legacy they want to leave. When a family does not want to discuss death openly, then, the legacies become projects. Thus, we make meaning but in an implicit rather than explicit way.

Bilingualism

Another ethical issue relates to all community collective work being carried out bilingually. I considered ideas regarding foreignizing narrative therapy for French first language speakers. polanco and Epston (2009) stated that as narrative ideas migrate cultures these crossings can enrich and diversify narrative practices (I shaped narrative practices for different cultures in the past; see Moxley-Haegert 2009). I consult with francophones for verification of the written language and cultural interpretation. This cultural and language environment provides me with an invitation to address privilege. While I hold privilege as the person consulted, I, as a minority anglophone am also in a less privileged position. When speaking to a francophone I often ask, "*Was that clear*?" "*Am I asking the questions that you want me to ask?"*

I give my notes saying, "*I want you to always know what is in your file. There will be spelling mistakes, but I would rather you knew what I write than hide my difficulties with written French*."

My experience with narrative practitioners is that we lead with questions; we ask if the questions are the ones the people consulting us want to respond to; we watch for discomfort and pull back when the person consulting us seems uncomfortable. I have learned from children and parents that they appreciate it when I follow their lead. The child goes back and forth from "open-awareness" to "mutual-pretense" over the time of our work together, as do family members.

I prepared questionnaires for all groups and workshops and after individual/family conversations and co-create the evaluative questions with the people who consult me. I apologize for my questions when a person seems uncomfortable or unable to answer and ask what they would like to talk about or rephrase the question. Continually asking if those who consult find this work helpful is ethically important.

Summary

With children, I use narrative and community practices to create songs, poems, films, art, letters, and music which record values, beliefs, and knowledges, archiving stories to be sent to friends and relatives. I use narrative practices such as Tree of Life workshops, questions of hope with wisdoms to be shared with our virtual group and individual narrative therapy projects. I named this "Leaving a Legacy" (Moxley-Haegert 2015). I use re-membering conversations to help families keep the child close to their hearts. Collective community work included archiving alternate stories in a living document called Little Steps, developing community by pairing parents with insider knowledges with newly bereaved parents, and sharing with them letters of stories and support. I named that, Letting the Legacy Live (Moxley-Haegert 2015).

What Was Appreciated about This Work?

When I asked Martine what could have been done differently in this work, she said: "*I felt respected and never judged. I never felt pressured, disturbed, or stressed by the process. I was given room to be creative in an intellectual way and I felt so much better after*."

I feel honored that I could be part of a therapeutic journey which could produce such a response. To me that is the important ethics of a beneficial conversation which can be created by narrative therapy. The Just Therapy group taught me that "*the values of humility, sacredness, respect, justice and love, trust and co-operation are absolutely central to (the) processes of accountability*" (Tamasese et al. 1995, pp. 109). I believe Martine's response suggested that I was following their wisdoms.

Key Take Home Messages

Facilitators of narrative therapy in cancer

Conversations can shape new realities and meanings of our lives.

Following the practice of developing identity by searching for stories that *counter* the problem story can lead to more positive experiences during difficult times.

Identity is strengthened by sharing which is a major part of the narrative practices in this work.

Developing **community, compassion, cooperation, and hope** were shown to have more positive psychological outcomes.

Interventions of narrative practice used in this work

Re-authoring.

Counter story development.

Collective narrative practices.

Definitional ceremonies.

Therapeutic documentation, i.e., living documents, narrative letters.

Narrative practices of subordinate storyline development.

Life as an identity project.

Meaning-making.

Re-membering conversations.

Areas for Further Research

1 There were two brief evaluations to understand whether the children and families found these narrative practice services helpful.

2 There is a need for much more research to be done with more patients and family members to determine if other narrative programs show similar positive results.

Trusted Websites for Further Reading

For further information on narrative practices and community work please refer to the following websites:
www.dulwichcentre.com.au
www.narrativeapproaches.com

Note

[1] Thanks to the families who gave permission for stories to be told using their children's first names and to the Petits Pas\ Little Steps members https://www.hopitalpourenfants.com/sites/default/files/PDFs/petit_pas_lr.pdf who ensured many legacies could live for us all.

References

Blueband-Langner, M. (1978). *The Private World of Dying Children*. Princeton: Princeton University Press.

Chez Nous (2010). *Pay It Forward: Remembering Angy*. Montreal: Montreal Children's Hospital Newsletter.

Denborough, D. (2008). *Collective Narrative Practice: Responding to Individuals, Groups and Communities Who Have Experienced Trauma*. Adelaide, Australia: Dulwich Centre Publications.

Epston, D. (2016). The Corner: re-imagining history for the future. *J. Syst Ther* 35 (1): 79–87.

Freeman, J., Epston, D., and Lobovits, D. (1997). *Playful Approaches to Serious Problems: Narrative Therapy with Children and Their Families*. New York: W.W. Norton.

Freud, S. (1961). Mourning and melancholia. In: *The Standard Edition of the Complete Psychological Works of Sigmund Freud* (ed. J. Strachey), 239–260. London: Hogarth Press.

Hedtke, L. (2014). Creating stories of hope: a narrative approach to illness, death and grief. *Int J Narrat Ther Community Work* 1: 3–10. doi:10.1002/anzf.1040.

Kubler-Ross, E. (1969). *On Death and Dying*. New York, N.Y: Scribner.

Marsden, D., Epston, D., and Markham, L. (2016). *Narrative Therapy in Wonderland: Connecting with Children's Imaginative Knowhow*. New York: W.W. Norton.

McPhie, L. and Chaffey, C. (1998). The journey of a lifetime: Group work with young women who have experienced sexual assault – The Dulwich Centre. https://dulwichcentre.au.com/articles-about-narrative-therapy/the-journey-of-a-lifetime.

Montreal Children's Hospital (2014). Little Steps/Petits Pas. https://www.hopitalpourenfants.com/sites/default/files/PDFs/petit_pas_lr.pdf.

Moore, K., Talwar, V., Gomez-Garibello, C. et al. (2020). Children's spirituality: exploring spirituality in the lives of cancer survivors and a healthy comparison group. *J Health Psychol* 25 (7): 888–899. doi:10.1177/1359105317737605.

Moore, K., Talwar, V., and Moxley-Haegert, L. (2015). Definitional ceremonies: narrative practices for psychologists to inform interdisciplinary teams' understanding of children's spirituality in pediatric settings. *J Health Psychol* 3: 259–272. doi:10.1177/1359105314566610.

Morgan, A. (2000). *What is Narrative Therapy? An East-to-Read Intriduction*. Adelaide, Australia: Dulwich Centre. ISBN10 0957792905. ISBN13 9780957792906.

Moxley-Haegert, L. (2009). Shaping narrative therapy to fit local cultures. *Int J Narrat Ther Community Work* 3: 55–70.

Moxley-Haegert, L. (2012). *Hopework. Stories of Survival from the COURAGE Programme: families and children diagnosed with cancer*. Available at: narrativetherapyonline.com/moodle/mod/resource/view.php?id=577.

Moxley-Haegert, L. (2015). Leaving a legacy and letting that legacy live. *Int J Narrat Ther Community Work* 2: 58–70.

Moxley-Haegert, L. (2018). Les petits pas: garder vivant l'héritage. In: *Dire bonjour à nouveau: L'approche narrative pour les personnes, les familles et les entreprises en deuil* (eds C. Mengelle and P. Blanc-Sahnoun), 105–122. Paris, France: Satas.

Moxley-Haegert, L. and Moxley Haegert, C. (2019) Little Steps Toward Letting the Legacy Live: fine Traces of Life to Accompany Families Grieving the Death of a Child, *Journal of Narrative Family Therapy*. Francophone Release. www.journalnft.com, pp. 28–52. Retrieved January 12 2020, https://www.journalcnt.com/archive-by-release.html.

Myerhoff, B. (1982). Life history among the elderly: performance, visibility and re-membering. In: *Reflective Perspectives in Anthropology* (ed. J. Ruby). Philadelphia: University of Pennsylvania Press. Retreived March 11 2004, doi: 10.9783/97815128064-006.

Ncube, N. (2006). The Tree of Life Project: using narrative ideas in work with vulnerable children in Southern Africa. *Int J Narrat Ther Community Work* 1: 3–16.

Newman, D. (2008). 'Rescuing the said from the saying of it: living documentation in narrative therapy. *Int J Narrat Ther Community Work* 3: 24–34. https://narrativetherapycentre.com/wp-content/uploads/2020/04/Rescuing-the-said-from-the-saying-of-it (accessed 19 January 2020).

Pilkington S. (2017). Deconstructing denial: stories of Narrative Therapy with people who are dying and their families, *J Narrat Fam Ther* 1: 54–75. www.journalnft.com. https://www.journalcnt.com/archive-by-release.html (accessed 01 March 2018).

Pilkington, S. (2018). Writing narrative therapeutic letters: gathering, recording and performing lost stories, *Journal of Narrative Family Therapy,* Special Release, www.journalnft.co, pp. 20–48. https://www.journalcnt.com/archive-by-release.html (accessed 11 March 2019).

polanco, M. and Epston, D. (2009). Tales of travels across languages: languages and their anti-languages. *Int J Narrat Ther Community Work* 4: 62–71.

Stevenson, M. (2014) *Being a bereaved parent: early bereavement experiences and perspectives on paediatric palliative care and bereavement services*. Unpublished doctoral thesis, University of Montreal, Quebec, Canada.

Tamasese, K., Waldegrave, C., Tuhaka, F., and Campbell, W. (1995). Furthering conversation about partnerships of accountability: talking about issues of leadership, ethic and care. *Just Therapy Journal,* Dulwich Centre Publications, 97–117.

White, M. (1988). Saying hullo again: the incorporation of the lost relationship in the solution of grief. In: *Selected Papers* (ed. M. White), 37–46. Adelaide, Australia: Dulwich Centre Publications.

White, M. (1998). *Re-authoring Lives: Interviews and Essays*. Adelaide, Australia: Dulwich Centre Publications.

White, M. (2001). Narrative practice and the unpacking of *identity* conclusions. *Gecko J Deconstr Narrat Ideas Ther Pract* 1: 28–55.

White, M. (2006). Responding to children who have experienced significant trauma: a narrative perspective. In: *Narrative Therapy with Children and Their Families* (M. White and A. Morgan), 85–97. Adelaide, Australia: Dulwich Centre Publications.

White, M. (2007). *Maps of Narrative Practice*. London: W.W. Norton.

White, M. and Epston, D. (1990). *Narrative Means to Therapeutic Ends*. New York, New York: W.W. Norton.

29 Nutrition for Cancer Prevention, Adjunctive Cancer Care, and Rehabilitation

Nutrition and Cancer

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[Aspects of Nutrition in cancer and cancer prevention are also discussed in Chapters 1 and 9].

Introduction

Diet is widely acknowledged as an important contributor to gastrointestinal cancer, in which up to 75% of colorectal cancer cases are associated with diet (Rafter 2003).

The "anticancer diet" does not constitute one simple "gold-standard" diet to follow. Instead, an individuals' diet must be carefully tailored to time, scale, type of cancer, and other co-morbidities.

The biggest consideration depends on the aim of the diet. There are three main aims of diets in relation to mitigation of cancer. Firstly, diet may be used for a ***primary prophylactic*** purpose to prevent the development of cancer. This can take the form of *primary prevention* aimed at the general population, or *secondary prevention* specifically aimed at premalignant high-risk groups. In the context of gastrointestinal cancer, the latter includes those suffering from precancerous conditions such as Barrett's esophagus or ulcerative colitis. Secondly, diet may be used as an ***adjunctive treatment*** alongside primary anticancer therapies. This may act either as a *supportive* cancer therapy to reduce the side effects of treatment or as an *adjunctive* cancer therapy to increase the likelihood of a favorable prognosis. Lastly, diet may be used to facilitate ***postcancer recuperation.*** This may act either as *supportive* cancer prevention to help the body recover from the adverse effects of anticancer treatment, or *tertiary* cancer prevention to prevent relapse of the cancer or metachronous lesions.

Supportive nutritional therapy comprises three types; oral, enteral, and parenteral. This chapter will not cover the latter two as the local and regional protocols and processes should be followed. In addition the various chemopreventative supplements known to have an effect on various cancer reduction from epidemiological studies will not be discussed either as they are reviewed comprehensively elsewhere (Jankowski and Hawk 2006).

Depending on these three aims – primary prophylaxis, adjunctive treatment, or postcancer recuperation – one's diet should differ accordingly. To satisfy the first aim, i.e., primary prophylaxis, one should prioritize maintaining the "goldilocks range" of macro- and micronutrients over the long-term. The second aim – preventing the exacerbation of a cancer during chemotherapy – should prioritize consuming foods which would not pose a danger to the weakened immune system. Thirdly, a postcancer diet should focus on replacing low vitamin and mineral levels, as well as increasing macronutrients commonly in deficit following treatment, such as proteins and fats.

Therefore, while those seeking a primary prophylactic aim should focus on what foods should be consumed, those seeking diet as an adjunctive therapy should focus on what foods to avoid.

Those in postcancer recuperation should focus on diets that can be tolerated sustainably.

Despite our focus on the benefits and dangers of specific micro- and macronutrients, obesity now acts as the greatest risk factor for cancer development (Jankowski 2008). Although obesity has other confounding variables, such as alcohol intake, comorbidities, genetic predisposition, and activity level, high fat and sugar diets promoting obesity will greatly increase cancer risk.

We must focus on what foods can be introduced to replace foods high in trans fats, refined carbohydrates, salt, and carcinogens to prevent cancer.

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A. Phyto-Prevention of Cancer

A healthy diet has five main food groups. These include ***oily fish*** rich in anti-inflammatory omega-3, ***whole proteins*** with all nine essential amino acids, water-soluble ***dietary fiber***, ***probiotics, 7 essential fatty acids,*** and finally a moderate intake of ***micronutrients*** including the 13 essential vitamins and 15 essential minerals.

Phyto-Prevention is a method of cancer prevention in which plant phytochemicals are ingested, most often through consumption of fresh produce such as vegetables, wholegrains, fruit, and fish. Oral supplementation of phytochemicals in capsular form may be used as an alternative, but not additional, method of oral administration. The effect of high supplementary doses of phytochemicals is still inconclusive, therefore over-supplementation is not recommended.

There is strong research evidence from epidemiological studies positively associating many phytochemicals with cancer prevention and prognosis; however, most intervention studies and randomized studies in this area are limited or inconclusive.

The main phytochemicals that have shown promising potential in cancer studies include phenols, carotenoids, and isoflavones.

Phenols are most commonly found in green tea, nuts, and berries. Isoflavones are most prevalent in soy products and legumes. Carotenoids are found in red and orange fruit and vegetables, like yams, carrots, and tomatoes.

Unfortunately, most clinical trials of phytochemicals, methodological limitations such as small sample sizes, insufficiently validated intermediate endpoints, and confounding factors mean that concluding that phytochemicals exhibit strong preventative effects against cancer is still not possible (Choudhari et al. 2020). Nonetheless there is encouraging evidence in a few select phytonutrients in prevention in specific cancers (see Table 1).

What are Inflammatory foods?

There are four main types of food associated with increased inflammation when consumed in large amounts:

- α-6 omega polyunsaturated fats
- Animal saturated fats and animal protein, especially in red meat and dairy products
- Artificial transfats in oils and crispy pastry and biscuits
- A high-salt diet is also associated with increased inflammation

These are known to exacerbate autoimmune diseases like multiple sclerosis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and Type 1 DM. These foods may also worsen cancers associated with

Table 1 The role of macronutrients and micro-phytonutrients in cancer prevention.

Dietary component	Highly recommended for protective and adjunct effects	Likely cancer protective but contraindicated in adjunct therapy	Further investigation required	Unlikely protective
Carbohydrate-related high fiber		Colorectal		Non-gastrointestinal cancer
High protein	Oily and white fish	Avoid if runny eggs, sushi, raw meat etc.	Soya and pulses	Protein supplements
Essential fatty acids – alpha 3 omega (esp. oily fish)	Colorectal			
Pro/pre/symbiotics		Colorectal		
Phytochemicals	Prostate		Lung adenocarcinoma and squamous cell carcinoma	
Phenolic acids				
Carotenoids (esp. lycopene)				
Isoflavones				
Salicylates	Colorectal cancer, esophageal adenocarcinoma	Avoid in gastric cancer to avoid GI bleeding	Gastric adenocarcinoma	Lymphoma
(Anti-inflammatory agents) selenium, vitamins A, C, D, E	Prostate, squamous cell esophagus			Beta carotene supplementation may increase cancer risk
Folate	If folate deficient	5-FU Trx	Pancreas	If normal levels
Minerals incl. zinc magnesium				If normal levels

chronic mucosal inflammation like colorectal cancer and Barrett's esophagus.

However, other lifestyle factors also exacerbate information, and cannot be ignored at the expense of a healthy diet. These include:

- Low levels of exercise (less than 30 min × 3 per week)
- Increased alcohol (>14 units per week, although the risk is noticeable in some at > 5 units per week)
- Any exposure to cigarette smoke (active and passive)
- Obesity (>BMI 25 and raised ×10 above BMI 40)

These agents have diverse pleiomorphic but as yet poorly elucidated aetiopathological pathways but at least in part through T-helper cell induction, thereby activating mucosal inflammation as well as dysbiosis and osmotic stress (especially in the case of salt).

The role of anti-inflammatory foods

The most studied anti-inflammatory foods include the **"SPACE"** food grouping:

- Selenium ("BONE" – Baked Beans, Oily Fish, Nuts, e.g. brazil, and Eggs)
- Phytochemicals ("BASK" – Berries, Avocado, Spinach, and Kale)
- Vitamin A and α-3 omega polyunsaturated fats
- Vitamin C
- Vitamin E

Their mechanism of action is well studied, including scavenging-free radicals and mitigating NFκB, PPAR-γ induction, macrophage activation, and leptin curtailment.

Dietary bacterial products come in the form of ***prebiotics*** (food for probiotic bacteria), ***probiotics*** (the bacteria themselves), and a combination of both, known as ***symbiotics***. Probiotic diets consist of live microorganisms usually added to fermented dairy products like yoghurts, or taken in capsule form (especially in those intolerant of dairy products). Kefir, from fermented milk, arguably a good option and is available in nondairy forms too (Coconut, Oat, Rice, Nut, and seed varieties). There has been much indirect evidence which links long-term consumption of probiotics to protection against colorectal cancer. Comparable benefits seem apparent with symbiotics.

B. Nutrition as Adjunctive Cancer Therapy

Altering diet can also increase cancer prognosis and reduce potential side effects during a course of anticancer therapy. Fiber aids GI motility, improves the microbiome lessening the risk of functional, inflammatory, and neoplastic diseases (Gill et al. 2021). Foods containing dietary fiber, such as wholegrains and cruciferous vegetables as well as pulses, have epidemiological evidence associated with a reduced risk of colorectal cancer over long-term use (Burkitt 1975). However, for people already suffering from, or at high risk of suffering from cancers that may induce bowel obstruction, such as colon, stomach or pancreatic cancers (Tuca et al. 2012), a high fiber diet is relatively, and in some cases absolutely, contraindicated, especially peri-surgery. So while an increased fiber consumption over a lifetime will facilitate healthy intestinal function and prophylaxis of colonic pathologies, intake when already at risk of colon cancer may exacerbate morbidity by increasing risk of malignant bowel obstruction (MBO) as well as post-prandial pain. Many patients during cancer therapy will also have altered bowel transit principally due to treatment and also due to opioid pain relief. So judicious use of fiber is needed, if at all in order to prevent intestinal pain and rarely blockage. Many physicians advise low fiber white bread and pasta when chemotherapy diarrhea occurs.

Probiotics including raw milk and blue cheese have been shown to have positive effects when used as a primary prophylactic. However, their use as an adjunctive anticancer therapy should be avoided. The reasons for this are that during cancer therapy most patients may be relatively immunosuppressed so exogenous bacteria in the diet could rarely lead to septicemia. However, inactivated probiotics may have a role with very low risk but efficacy as yet undefined.

There is conflicting evidence about coadministration of folic acid with certain chemotherapy regiments. Leucovorin (a folate analogue) enhances 5-Fluoro-uracil action, whereas folic acid inhibits the action occasionally of agents like docetaxel.

Alcohol, except in moderation (<6 units pw), can interfere with certain chemotherapy agents like procarbazine. In addition, there is a synergistic action of alcohol with opiate analgesics, antidepressants, and anti-emetics which can induce extreme drowsiness, dizziness, and poor coordination. Alcohol can also aggravate nausea, a very common side effect during chemotherapy, by increasing fatty liver.

Ensure to encourage good intake of water and regular snacks especially high in protein.

C. Postcancer Care Nutritional Rehabilitation/Support

The third and final purpose of an anticancer diet is to help restore the body to a state of health seen before the adverse effects of both cancer and primary anticancer therapies occurred.

This can be achieved in two main ways.

Firstly, restoring the appropriate levels of macronutrients, namely protein and healthy fats, will help to combat muscle atrophy, edema, and increased susceptibility to infections caused by anticancer therapies. Healthy fats include monosaturates (olive oil) and polyunsaturates (sunflower, linseed, and fish oil).

Secondly, restoring diminished levels of micronutrients will overcome other common side effects of anticancer therapy, especially anemia (B12, Folate, and Ferritin), fatigue (electrolyte deficiencies), and parathesiae or myopathy (vitamin D and trace element deficiencies).

In the weeks following chemotherapy, it is likely that gastrointestinal disturbances will be experienced. Following radiotherapy or surgery, these disturbances, namely diarrhea, are likely to be more prevalent and long-lasting. Unfortunately, these lasting effects are largely unavoidable; however, the best way to reduce the severity of these effects is through adaptation of one's post-therapy diet. These adaptations involve careful monitoring of both micro- and macronutrients mentioned above. There is weak evidence that aminosalicyltes, cholestyramise balsazide, rectal sucralfate, and oral budesonide are beneficial in preventing these effects. In very extreme cases, oral prednisolone as well as selective surgery are most likely effective. However, most cases respond to low residue diets which are low in exacerbating factors, namely lactose and legumes, which unmask irritable bowel syndrome (IBS) as well as symptomatic use of anti-diarrheal agents like loperamide.

Careful monitoring of macronutrients will reduce the severity of diarrhea, while micronutrients will help replace the fluids and essential minerals lost through diarrhea.

Plain food that contains little insoluble fiber such as white rice or pasta, peeled potatoes, or unfried white meats should be consumed, as well as fruits especially berries. These should replace wholegrain, high-fiber foods such as rye bread, pulses, or brown rice. Meals should be prepared avoiding frying with oil, with fatty foods being restricted.

One should also avoid food additives which are known to stimulate faster GI activity. This includes foods containing caffeine such as black tea, coffee, or cola, as well as hot spices and strong flavors.

Empirically, drinking herbal teas such as chamomile can be beneficial as they contain less caffeine and may help in reducing abdominal pain associated with intestinal disturbances. Other fluids, such as electrolyte-replacing drinks and pure fruit juices will help to replace both the water and micronutrients lost from diarrhea. Ensure to drink at least 4 8-ounce (250 ml) glasses of water per day to maintain kidney and cardiac function.

Sticking to these dietary recommendations, alongside gentle aerobic exercises such as walking, can produce a synergistic effect in promoting healthy GI activity.

Summary Box

What we know:

a Salicylates are recommended for cancer prevention
b Fiber is recommended for colorectal cancer prevention
c Protein consumptions aids for cancer support
d Avoid probiotics in immunosuppressed groups
e α-3 omega essential fatty acids act as anti-inflammatory agents
f There exists a long term association of Mediterranean, pescatarian and vegetarian diets with preventing cancer
g Alcohol greater than 6 units per week is deleterious to cancer prevention

Current gaps for prospective research

a The role of nutritional supplements for specific cancer prevention or cancer support
b The role of special commercially available (non-dietician prescribed) liquid drinks
c The risk of probiotics in cancer therapy

National Evidence-based Guidelines and Useful Links

- https://www.cancer.gov/about-cancer/causes-prevention/risk/diet
- https://www.cancerresearchuk.org/about-cancer/bowel-cancer/living-with/eating
- https://www.hopkinsmedicine.org/health/conditions-and-diseases/cancer/cancer-diet-foods-to-add-and-avoid-during-cancer-treatment
- https://www.health.qld.gov.au/__data/assets/pdf_file/0022/152473/gastro-obstruct.pdf

References

Burkitt, D.P. (1975). Large-bowel cancer: an epidemiologic Jigsaw puzzle. *J Natl Cancer Inst* 54 (1): 3–6.

Choudhari, A.S, Mandavi P C, Deshpande M, Ranejekar P, Prakash O. (2020). Phytochemicals in cancer treatment: from preclinical studies to clinical practice. *Front Pharmacol* 10: 1–82.

Gill, S.K., Rossi, M., Bajka, B. et al. (2021). Dietary fibre in gastrointestinal health and disease. *Nat Rev Gastroenterol Hepatol* 18: 101–116. https://doi.org/10.1038/s41575-020-00375-4.

Jankowski, J. (2008). Round table discussion: nutrition and cancer prevention. *Int J Probiotics Prebiotics* 3 (3): 169–170.

Jankowski, J.A. and Hawk, E.T. (2006 Feb). A methodologic analysis of chemoprevention and cancer prevention strategies for gastrointestinal cancer. *Nat Clin Pract Gastroenterol Hepatol* 3 (2): 101–111. doi:10.1038/ncpgasthep0412.

Rafter, J. (2003). Probiotics and colon cancer. *Best Pract Res Clin Gastroenterol* 17 (5): 849–859.

Tuca A., Guell E, Martinez-Losada E, Codorniu N. (2012). Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. Cancer Management and Research, 159.

Cancer – The Road Less Traveled

Quotes about Cancer Perspectives from Those Who Preceded You!

> Cancer is never the preferred fork in the road, but love and hope sustain you on the journey.
>
> – Margaret Jankowska

> If you save one life, it's as if you have saved the entire world.
>
> – Old Testament

> You beat cancer by how you live, why you live and the manner in which you live.
>
> – Stuart Scott

> A hero is an ordinary individual who finds the strength to persevere and endure in spite of overwhelming obstacles.
>
> – Christopher Reeve

> Remembering that I'll be dead is the most important tool I've ever encountered to help me make the big choices in life. Almost everything, all external expectations, all pride, all fear of embarrassment or failure - these things just fall away in the face of death, leaving only what is truly important. Remembering that you are going to die is the best way I know to avoid the trap of thinking you have something to lose. You are already naked.
>
> – Steve Jobs

Survivor, Just doesn't mean staying alive, it means living to your full potential for as long as you can.

– Antoinette

I intend to appreciate, marvel and enjoy all the time I have left, with or without cancer.

– Saskia Lightstar

Advice for people with Cancer, "if I had to summarise it in one word it would be HOPE. Never loose hope.

– Brett Cordes

Grant me the serenity to accept the things I cannot change, courage to change the things I can, and wisdom to know the difference.

– The serenity prayer

You have to be willing to give up the life you planned, and instead, greet the life that is waiting for you.

– Joseph Campbell

Yesterday is history, tomorrow is a mystery, but today is a gift – that's why it's called 'the present'.

– Eleonor Roosevelt

Faith is the bird that sings when the dawn is still dark.

– Rabindranath Tagore

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When you are sorrowful, look again at your heart, and you shall see that in truth you are weeping for that which has been your delight.

– Kahil Gibran

It takes great strength to make your way through grief, to grab hold of life and let it pull you forward.

– Patti Davis

We cannot get through life without pain. What we can do is choose how to use the pain that life presents us.

– Bernie S. Siegel

We must embrace pain and use it as fuel for our onward journey.

– Kenji Miyazawa

What does not kill us makes us stronger.

– Friedrich Nietzsche

Attitude is a little thing that makes a big difference.

– Winston Churchill

Life isn't about waiting for the storm to pass, its about learning to dance in the rain.

– Vivian Greene

Just when the caterpillar thought its life was over, it became a butterfly.

– Chuang Tsu

We cannot direct the wind, but we can adjust the sails.

– Thomas Monson

The mind is everything, what you think you also become.

– Budda

I believe in one thing—that only a life lived for others is a life worth living.

– Albert Einstein

Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.

– Albert Einstein

Additional Resources

https://pancan.org/news/survivors-favorite-quotes
https://www.thequotesflix.com/inspirational-quotes-for-cancer-patients
http://www.planetofsuccess.com/blog/2019/cancer-quotes

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